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VENTRICULAR TACHYCARDIA

AN ANALYSIS OF THIRTY-SIX CASES

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Paroxysmal ventricular tachycardia is a rare condition. Numerous articles have, however, been published on the subject, although detailed case reports from a single hospital have not exceeded 6. In two articles Strauss [1] and Lundy and McLellan [2] reported a few cases and analyzed the literature. We here present and discuss 36 cases, to the best of our knowledge the largest series from one hospital.

The files of the Heart Station at the Boston City Hospital contain approximately 64,000 electrocardiograms taken over a period of twenty years. Seventy cases are listed in the cross index files under the diagnosis of ventricular tachycardia. Of this number we discarded 34 because the diagnosis was not certain. This makes the incidence of ventricular tachycardia 1 in every 1,800 tracings, confirming the general impression that the condition is rare. The patients were cared for by the various services of the hospital, and in only a few instances were they personally examined by us.

CRITERIA FOR THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF VENTRICULAR TACHYCARDIA

Although sometimes ventricular tachycardia can be suspected by direct clinical observation, the diagnosis can be made with assurance only by means of the electrocardiogram. In some cases even then the diagnosis, though likely to be correct, is not beyond all doubt. The essential

Read at the meeting of the New England Heart Association, Boston, March 24, 1941.

From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services of the Boston City Hospital and the Department of Medicine, Harvard Medical School.

1. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, Am. J. M. Sc. **179**:337, 1930.

2. Lundy, C. L., and McLellan, L. L.: Paroxysmal Ventricular Tachycardia: An Etiological Study with Special Reference to the Type, Ann. Int. Med. **7**:812 1934.

point is to demonstrate an ectopic ventricular origin of the ventricular pacemaker, which always causes a prolonged QRS interval. Such ventricular complexes may, however, be produced in auricular and nodal tachycardia and even auricular flutter,[3] if there is a temporary aberrance of ventricular conduction, and can simulate ventricular tachycardia very closely, especially when the P waves are obscure. Any supraventricular tachycardia in the presence of permanent bundle branch block may produce the same picture.

In ventricular tachycardia the auricles may be stimulated by retrograde conduction to beat after each ventricular contraction or after every second beat. In the early work on the experimental production of ventricular tachycardia in dogs, Lewis [4] showed that such retrograde conduction can take place, and instances of its occurrence in man have been reported.[5] It is probable, however, that the usual mechanism is for the auricles to maintain an independent rhythm, usually slower than the ventricular rate. This was demonstrated in man by Palfrey,[6] who in 1913 showed by polygraphic tracings such an independence of the auricular and ventricular rhythms.

A diagnostic point of primary importance is therefore the demonstration of an independent auricular rhythm, usually at a slower rate. It may, however, be impossible to discern this, because the P waves are obscured by the QRS complexes or T waves, because of retrograde auricular conduction or because of the existence of auricular fibrillation.

The taking of a special auricular precordial lead is often helpful in demonstrating P waves when the other leads fail to bring them out. Although Lewis and others have used similar leads in the study of auricular rhythm, no reference to their use in ventricular tachycardia has appeared in the literature on that subject to our knowledge. Procedure for the taking of the special auricular lead was worked out in this department by Dr. J. M. Faulkner [7] and is followed routinely in the diagnosis of obscure disorders of rhythm. It has repeatedly cleared up an otherwise doubtful diagnosis (fig. 1). The lead is taken by placing

3. Marvin, H. M., and White, P. D.: Observations on Paroxysms of Tachycardia, Arch. Int. Med. **29**:403 (April) 1922.

4. Lewis, T.: Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, Heart **1**:98, 1909; Mechanism of the Heart Beat with Especial Reference to Its Clinical Pathology, London, Shaw & Sons, 1911, pp. 24, 168, 258 and 276.

5. Hart, T. S.: Paroxysmal Tachycardia: The Paroxysms Arise from Impulses of Ventricular Origin; the Auricle Responds to the Ventricle; Evidence of Two Points of Ventricular Irritability, Heart **4**:129, 1912. Scott, R. W.: Observations on a Case of Ventricular Tachycardia with Retrograde Conduction, ibid. **9**:297, 1922.

6. Palfrey, F. W.: Paroxysmal Tachycardia Confined to the Ventricles or to the Auricles, with Illustrative Cases, M. & S. Rep. Boston City Hosp. **16**:182, 1913.

7. Faulkner, J. M.: Unpublished data from the Heart Station, Boston City Hospital.

the left arm electrode in the third interspace at the right sternal border and exposing the film with the lead switch first in "Lead I" position and then in "Lead III" position. Thus, first the right arm and then the left leg is used as the indifferent electrode. In many cases, P waves are well shown in one of these special leads but not in the other.

Further evidence of the true nature of ventricular tachycardia may be found in control records taken before or after an attack, in the registration of the beginning or cessation of the paroxysm or in the demonstration of extrasystoles having the same appearance as the ventricular complexes seen in the attack.

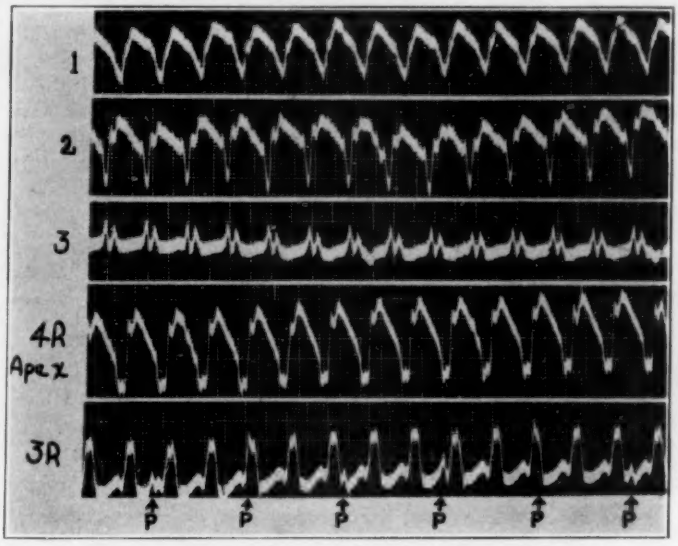

Fig. 1.—Paroxysmal ventricular tachycardia. The special auricular lead (marked 3R) shows P waves which do not appear in the standard leads. The auricular rate is 63; the ventricular rate, 150.

It is difficult to lay down absolute rules for diagnosis. The demonstration of an independent auricular rhythm is certainly sufficient. If this cannot be shown, one should have control records. In rare instances one can diagnose the condition with reasonable certainty from the bizarre nature of the ventricular complexes alone, but except in such rare instances other evidence is needed.

A more detailed discussion of the criteria for the diagnosis of ventricular tachycardia will be found in other articles.[8]

8. Lundy and McLellan,[2] Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, Heart **8**:59, 1921. Wolferth, C. C., and McMillan, T. M.: Paroxysmal Ventricular Tachycardia: Report of One Case with Normal Mechanism and Three with Auricular Fibrillation, Arch. Int. Med. **31**:184 (Feb.) 1923.

RESULTS

Persistent Versus Intermittent Tachycardia.—For the purpose of analysis, the cases of ventricular tachycardia in our series were divided into two types. In the majority of tracings taken during an attack, all beats appeared to be of ventricular origin and each record presented a fairly uniform appearance (fig. 2). This group was arbitrarily designated "persistent" ventricular tachycardia. In one third of the cases, runs of ventricular tachycardia were separated by periods of normal rhythm, the latter often showing ventricular extrasystoles. Cases showing this type of tracing were called "intermittent" ventricular tachycardia (fig. 3). The subdivision of ventricular tachycardia on this basis is of course purely arbitrary, and it is quite possible that 1 case might show

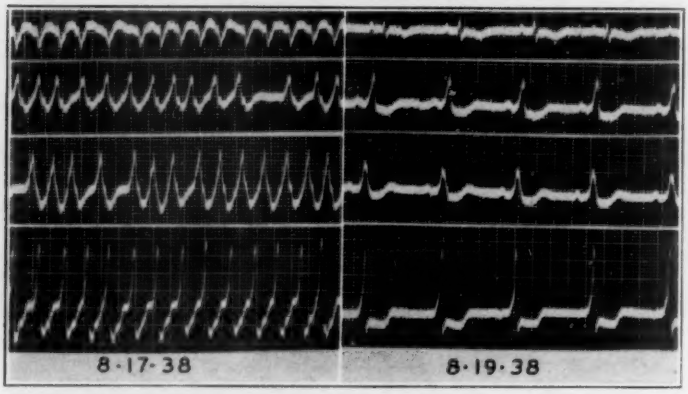

Fig. 2.—Ventricular tachycardia of the persistent type, showing slight irregularity of the ventricular rhythm. The control record, taken two days later, shows intraventricular block (QRS 0.12 second) and slightly prolonged Q-T interval (quinidine effect [?]). The T waves, which suggest digitalis effect, became normal in subsequent records.

each type of tracing if records were taken at appropriate times. However, in all cases in which several records were taken during the attack, the rhythm was consistently of one type or the other. This classification aids the study of the duration and prognosis of attacks and the results of therapy.

Twenty-four cases (66 per cent) were classified as persistent ventricular tachycardia. It was possible to demonstrate an independent auricular rhythm in 11 patients; of the remaining 13, 6 showed auricular fibrillation in records taken before or after the attack, and 7 showed no P waves during the attacks. The special auricular lead was not used in this department until 1937, and it is possible that P waves might have been

demonstrated by the use of that technic in some of the earlier records. Control records were available for comparison, however, in all but 1 of these 7 cases.

In no case was retrograde conduction to the auricle demonstrated. The proof of such conduction depends on the simultaneous recording of pulse tracings. This was not done in any of our cases.

Twelve cases (33 per cent) were classified as intermittent ventricular tachycardia. Normal strips in the same record for comparison with the tachycardia made the diagnosis easier, and an independent auricular rhythm could be more readily identified. Most of the records showed ventricular extrasystoles, and all showed abrupt onset or cessation

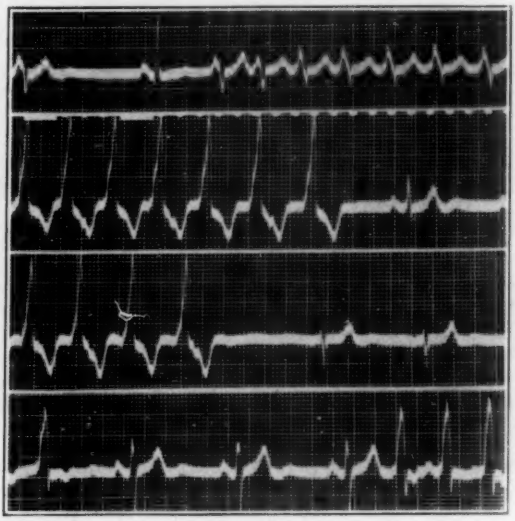

Fig. 3.—Ventricular tachycardia of the intermittent type. A run of ventricular tachycardia can be seen in each lead. The auricular rhythm is undisturbed and is easily identified through the periods of tachycardia.

of the tachycardia. Although technically ventricular tachycardia may be considered to be present when two or more ventricular extrasystoles occur in rapid succession, we have included cases in the series only if the run of tachycardia persisted for at least ten beats; in the majority of cases it was longer.

The incidence of auricular fibrillation as shown by control records (39 per cent) compares with that observed by Strauss [1] in his analysis of a large number of cases taken from the literature on ventricular tachycardia. It is interesting to observe that 2 patients with the intermittent type of tachycardia who showed auricular fibrillation before and during

the attack returned to normal sinus rhythm within five and fourteen days respectively after the end of the attack. One patient received quinidine; the other did not.

Detailed Analysis of the Electrocardiograms (table 1).—In the majority of cases records taken before or after the attack during the same hospital admission were available for comparison. In 27 cases more than one record was taken; five or more were taken in 10 cases, and in 1 case thirteen were taken.

Ventricular rates ranged from 110 to 250. In 32 cases the ventricular rate was faster than 130; in 10 it was faster than 170, and in 5 it was faster than 200. The two patients with the most rapid rates, 250 and 220 per minute, which were present on admission and persisted eight hours and two days after admission respectively, recovered and were discharged improved.

TABLE 1.—*Associated Electrocardiographic Abnormalities*

	Number of Cases	Percentage of Total
Auricular fibrillation	14	39
Shifting auricular pacemaker	2	6
Disturbances in conduction (in control records)		
Complete heart block	1	4
Incomplete auriculoventricular block	1	4
Intraventricular block (QRS = 0.11 - 0.12 sec.)	7	19
A-V dissociation	1	4

The duration of QRS ranged from 0.12 second to 0.20 second. In 20 cases it was more than 0.14 second.

Records were examined to determine the regularity of the ventricular rhythm, because slight irregularity to auscultation is one of the points on which the diagnosis of ventricular tachycardia without the aid of the electrocardiogram is based.[9] The brief period during which a record is taken does not of course necessarily indicate what may occur over a longer period. In 1 case in which a continuous tracing was taken for five minutes, the record was regular except for three brief periods in each of which one ventricular beat was apparently "dropped."

In the 24 cases of the persistent type, only 4 records showed obvious irregularities of the ventricular rhythm (fig. 2). All but 1 showed a striking uniformity in the appearance of the ventricular beats, indicating uniformity in the point of origin. In 1 case there was a temporary irregularity in the appearance of the QRS complexes.

Of the 12 patients with the intermittent type, all but 1 showed uniform, regular QRS complexes during runs of ventricular tachycardia.

9. Levine, S. A.: The Clinical Recognition of Paroxysmal Ventricular Tachycardia, Am. Heart J. **3**:177, 1927.

The exception was our only patient with the alternating bidirectional type which is usually attributed to the toxicity of digitalis.[10]

Disturbances in Conduction.—In our series the incidence of disturbances in conduction was rather low (table 1). All disorders so listed were shown in control records before the onset of the paroxysm except intraventricular block, in cases of which the controls were taken after

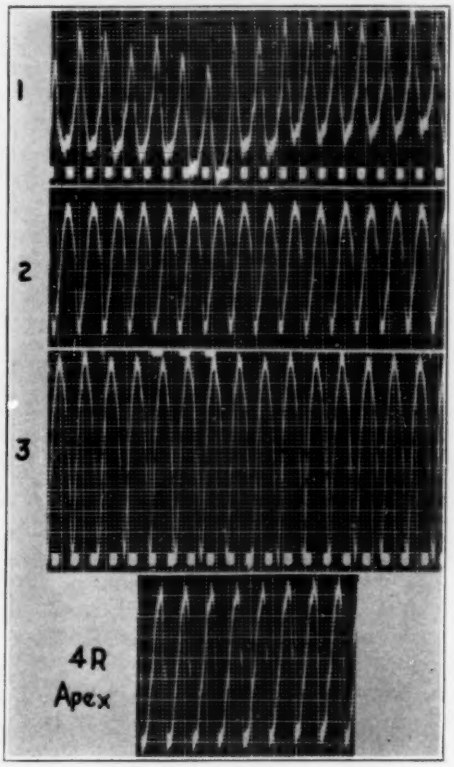

Fig. 4 (July 9, 1940).—Persistent ventricular tachycardia (rate 250) showing striking regularity of oscillation.

10. (*a*) Palmer, R. S., and White, P. D.: Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in the Direction of the Ventricular Complexes in the Electrocardiogram, ibid. **3**:454, 1927. (*b*) Marvin, H. M.: Paroxysmal Ventricular Tachycardia with Alternating Complexes Due to Digitalis Intoxication, ibid. **4**:21, 1928. (*c*) Scherf, D., and Kisch, F.: Ventricular Tachycardias with Variform Ventricular Complexes, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **2**:73, 1939.

the paroxysm. No cases of bundle branch block were encountered in this series. However, the low incidence of observed disturbances in conduction is not necessarily significant, because the time between control records and those taken during the attack varied greatly. Some were taken weeks or longer before or after the attack.

Relation to Age and Sex.—The preponderance of the older age groups is striking. Ninety-four per cent of the patients were over 40 years of age, and 52 per cent were over 60. Three fourths of the attacks occurred in men. These findings agree in general with those published in other series, but differ in that in our series there is no patient under the age of 30.

Underlying Heart Disease (table 2).—In only 1 case could it be definitely said that there was no underlying heart disease. The patient

TABLE 2.—*Underlying Heart Disease* *

No heart disease	1 case
Definite evidence of underlying heart disease	35 cases
Congestive failure	31 cases

Distribution of Types of Heart Disease

	Cases	Percentage	Autopsy
1. Arteriosclerotic	17	47	3
2. Hypertensive	4	13	..
3. Hypertensive and arteriosclerotic	11	31	4
4. Rheumatic	1	3	..
5. Rheumatic and hypertensive	1	3	..
6. Syphilitic	1	3	1
	35	100	8

* In groups 1 and 3 together, there were 6 definite instances of acute myocardial infarction (4 proved by autopsy). In 2 more instances this was a good possibility.

had a normal cardiac history; the results of physical examination were normal, and a teleoroentgenogram of the heart was also normal. She was the next to the youngest in the series (aged 37), and the precipitating cause of her attacks of ventricular tachycardia was unknown. The attacks of tachycardia were of the intermittent type and had apparently occurred for many years.

Another patient, the youngest, aged 34, was a woman with an enlarged heart, a loud apical first sound and systolic murmur and slight hypertension, but with no cardiac disability except palpitation and a sense of oppression in the chest during her attacks, which had occurred for at least two months and probably for much longer and were also of the intermittent type. She was considered to have rheumatic and hypertensive heart disease with involvement of the mitral valve. All of the other patients showed cardiac enlargement, disorders in rhythm or clear evidence of cardiac failure. The underlying heart disease was called arteriosclerotic in those patients of the proper age who showed any of

the disorders just mentioned or angina pectoris or myocardial infarction in the absence of any other possible cause for the disorder. The usual criteria were used in classifying the other cases as they are listed.[11]

As might be expected from the age distribution, so-called degenerative heart disease was present in 28, or 78 per cent, of the patients. Only 4 patients had unmistakable valvular involvement. Two of these had rheumatic mitral disease, 1 calcareous aortic stenosis and 1 syphilitic aortitis with aortic insufficiency and aneurysm of the ascending aorta. Many other patients had systolic murmurs without other evidence of valvular disease.

A number of cases of paroxysmal ventricular tachycardia occurring in persons without heart disease have been reported in the literature. It is probable that our series does not give a true indication of the relative occurrence of ventricular tachycardia in persons with and without heart disease. Most of our records were from hospitalized patients whose attacks had persisted long enough to permit the taking of an electrocardiogram. Persons without organic heart disease are likely to have attacks of short duration and are less likely to be studied in an attack.

Congestive Heart Failure.—The incidence of congestive failure in this series was high. The figure given in table 2 (86 per cent) refers to the percentage of patients with failure at the time of admission. In 8 of these ventricular tachycardia was present on admission; so it is not known whether the failure or the tachycardia came first. In 23 cases failure preceded the attack of ventricular tachycardia. In no patient could it be definitely shown that the attack precipitated congestive failure, although the failure was aggravated during the tachycardia in at least 2 cases. These facts are not surprising in view of the high percentage of underlying heart disease and the importance of toxicity due to digitalis as a precipitating factor in this type of tachycardia. Five of the 9 cases in this group were of the persistent type of tachycardia.

Precipitating Factors (table 3).—Toxicity due to digitalis was associated with the attack more often than any other single factor. We included in this group only those patients that had received at least twice the dose theoretically necessary for digitalization. In 3 cases definite symptoms of toxicity were recorded (nausea, vomiting, yellow vision). Four of the 8 cases in this group were of the persistent type of tachycardia.

In the group labeled "digitalis (?)" dosage of the drug was somewhat in excess of the theoretic requirement, and no other cause for the attack was apparent.

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11. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Heart Association, 1939.

One patient who had had excessive doses of digitalis had also received quinidine sulfate in large amounts (60 to 100 grains [3.88-6.48 Gm.] daily for four days) before the onset of the attack. In his case either drug or both in combination may have been a factor in precipitating the attack.

Acute myocardial infarction was present at the time of the attack in 6 cases; in 4 infarction was proved by autopsy and in the other 2 it was clinically evident and supported by classic changes in the electrocardiogram. Although the statement has been made that when ventricular tachycardia occurs in association with myocardial infarction it usually follows the administration of digitalis, only 2 of our 6 patients with myocardial infarction had received digitalis before the onset of ventricular tachycardia, and these had not had an excessive dose.

The group labeled "myocardial infarction (?)" presented suggestive but not conclusive evidence in the absence of other known cause.

Only 1 patient in our series had two distinct proved prolonged attacks of ventricular tachycardia. These were separated by a time interval of eight months. The patient died during the second attack, and autopsy revealed recent and healed myocardial infarctions. However, only the second attack was considered to have definite relationship to an acute infarction, because the time relationship of the first was somewhat uncertain. In the majority of cases the tachycardia followed infarction within a few days.

The "miscellaneous" group included 5 patients in whom an acute episode bore a close time relationship to the onset of the attack. The associated acute episodes were an injury received in an automobile accident followed by a fight, a cerebral vascular accident, uremia, cholelithiasis and an embolus to the femoral artery. No attempt will be made to evaluate this association.

Outcome of Attacks and Mortality (table 3).—There were 21 deaths during or after the attack of ventricular tachycardia (67 per cent), but only 8 patients died in the attack itself.

Although the duration of attacks during hospitalization (5 attacks were present on admission) of these 8 patients varied from four hours to five days, it was impossible to prove that the length of the attacks affected the mortality. The patients who recovered from the attacks and were discharged improved had in many instances attacks of equal or longer duration, although, with an exception to be noted, no attack lasted longer than nine days after admission.

One patient deserves special mention, since her attack lasted for six weeks. She was a woman aged 74 with severe degenerative heart disease. The attack developed without known precipitating cause seven weeks after an exploratory laparotomy, and during the six weeks it per-

sisted at a rate varying from 137 to 167 she complained only of weakness and palpitation. After the attack had commenced she was given about 27 to 36 grains (1.75-2.33 Gm.) (exact quantity uncertain) of digitalis in three days and was then maintained on a daily dose of 1½ grains (0.09 Gm.) for four weeks thereafter. Quinidine was given in varying amounts, with a maximum of 40 grains (2.59 Gm.) daily for seven days from the twenty-third to the thirtieth day of the attack. After spontaneous cessation of the attack her condition was but little altered. Pneumonia then developed, and she died a week later. Permission for autopsy was refused.

In our series there was no demonstrable relationship between mortality and heart rate, width of QRS or the type of the complexes, whether they were of the left or the right ventricular type.

TABLE 3.—*Probable Precipitating Factors Associated with Thirty-Seven Attacks in Thirty-Six Patients with Ventricular Tachycardia*

	Persistent Type			Intermittent Type			
Precipitating Factors of Ventricular Tachycardia	Died in Attack	Died Later in Hospital, Within 1 Month	Recovered	Died in Attack	Died Later in Hospital, Within 1 Month	Recovered	Total Attacks
Digitalis	1	3	0	0	2	2	8
Digitalis and quinidine	0	0	1	0	0	0	1
Digitalis (?)	2	1	1	1	1	3	9
Myocardial infarction	3	2*	0	0	1	0	6
Myocardial infarction (?)	0	0	3	0	0	0	3
Miscellaneous	1	1	3	0	0	2	5
Unknown	0	2	1	0	0	2	5
Total	7	9	9	1	4	7	37

* One of these patients died of a fresh myocardial infarction two months after the attack stopped.

What does influence the prognosis is the nature and degree of underlying heart disease. This is brought out most clearly in an examination of the mortality figures in the cases in which the precipitating factors were digitalis and myocardial infarction respectively. All 6 of the patients with definite myocardial infarction died, 3 of them in the attack, although the 3 in whom cardiac infarction was doubtfully present recovered. Six of the 8 who had had marked overdosage with digitalis also succumbed, though only 1 died in the attack. Five of the 9 to whom a moderate overdosage of the drug had been given also died. All of these patients had severe heart disease. In contrast, the patient with no heart disease is alive and well except for her attacks, as is the patient with probable mitral stenosis, who has had intermittent attacks for two months or longer; and 3 of the 5 in whom attacks occurred in association with noncardiac acute episodes are also living, the other 2 having died of uremia and cerebral hemorrhage respectively.

In general the intermittent type of tachycardia carried a somewhat less serious prognosis than the persistent type, since 7 of the patients with the former type survived, in contrast to but 9 of 24 of those with the latter. Moreover, in instances in which overdosage with digitalis may have been a factor, 9 patients had the persistent type and 7 died, and 9 had the intermittent type and only 4 died.

Quinidine Therapy.—The results of quinidine therapy are very difficult to evaluate because the patients were not uniformly treated or studied with especial care, because the dosage of quinidine was rather low and because of the possibility of spontaneous cessation of the attack. For these reasons it seemed unprofitable to analyze in detail the results of quinidine therapy in our series. Of the 24 patients with persistent tachycardia (25 attacks), 15 received quinidine but to only 12 of the latter (13 attacks) was it given in significant amounts (average of 15 grains [0.97 Gm.] to 70 grains [4.53 Gm.] daily, with a mean of 24 grains [1.55 Gm. of quinidine sulfate]). The duration of attacks after the initiation of quinidine therapy ranged from eight hours to four weeks and appeared to be fully as long as or longer than that of the untreated attacks. Seven of the 12 patients (13 attacks) receiving quinidine recovered; 3 died in the attack and 3 in the hospital subsequent to the attack. Two of the 11 patients receiving little or no quinidine recovered; 4 died in the attack and 5 after its cessation. Too many factors were involved to permit the drawing of any conclusions as to the efficacy of quinidine in this series.

Only 2 of the patients with the intermittent type of tachycardia were given quinidine in more than minimal doses. One died in the attack; the attack of the other stopped in twenty-four hours and recovery occurred.

One patient in whom ventricular tachycardia developed four days after a cerebral accident was given an unspecified amount of a 3 per cent solution of a quinine salt intravenously, and the attack ceased two hours after the injection was stopped. The patient died of the effects of the cerebral episode a day later.

It has been observed that quinidine often produces a slowing of the ventricular rate during the paroxysm of tachycardia. This phenomenon was studied by observation of the ventricular rate in the electrocardiogram. Of the 14 patients whose attacks were treated with quinidine, 4 had only one record taken during the paroxysm and 3 showed no slowing of the ventricular rate. In the other 7 definite slowing was observed, the minimum being 9 beats per minute, the maximum 112 beats and the mean 24. It would have been interesting to compare these findings with those of a similar group of untreated patients, but only one electrocardiogram was taken during the attack for each untreated patient. However, there were 2 patients who did not receive quinidine until the sixth and

the thirteenth day of the attack respectively. In the first the ventricular rate increased 9 beats per minute, and in the second it decreased 12 beats, in the time intervals mentioned. After quinidine was given, the rhythm in the first patient returned to normal, and in the second the ventricular rate slowed 22 beats per minute in four days' time.

COMMENT

It is generally agreed that toxicity due to digitalis and myocardial infarction are precipitating factors of ventricular tachycardia and that myocardial disease is present in most cases. Formerly hyperirritability of the myocardium induced by any of these factors was emphasized as the provoking cause. This was thought to create a center of excitation in one or several places in the ventricle. Circus movement of the exciting impulse in the ventricle has been suggested as the cause of ventricular tachycardia of the alternating bidirectional type.[12] Davis and Sprague [13] in reporting a case from this hospital [14] suggested that ventricular fibrillation, and possibly ventricular tachycardia, might be the result of a circus movement in the ventricles. Occasional records seem to support this thesis. One of our tracings shows a perfectly regular wavelike oscillation of the ventricular impulse at a rate of 250 per minute (fig. 4), but the rapid rate may account for the wavelike oscillation. It is also of interest that in this case intraventricular block was shown in subsequent control records. Davis and Sprague expressed the opinion that the conduction system of the ventricle normally tends to prevent circus movement because of its ability to conduct impulses rapidly to all parts, and that factors which depress the His-Purkinje system remove this inhibiting influence. Davis [15] discussed the relation of digitalis toxicity, bundle tissue disease (bundle branch block) and myocardial infarction to ventricular tachycardia. He expressed the opinion that the depressing effect of digitalis on auriculoventricular conduction time preceding ventricular tachycardia,[16] as well as the possible temporary disturbance in the conduction system in myocardial infarction, might be related to the arrhythmia. Herrmann and Ashman [17] expressed somewhat similar ideas with

12. Palmer and White.[10a] Marvin.[10b]

13. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, Am. Heart J. **4**:559, 1928.

14. This case is not included in our series.

15. Davis, D.: Ventricular Tachycardia: An Interpretation of the Nature of Its Mechanism, Am. Heart J. **7**:725, 1932.

16. Luten, D.: Clinical Studies of Digitalis, Arch. Int. Med. **35**:74 (Jan.) 1925.

17. Herrmann, G. R., and Ashman, R.: Partial Bundle Branch Block: A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle Branch Block, Am. Heart J. **6**:375, 1931.

regard to bundle branch block. Miller [18] has recently presented a good summary of the state of opinion on this question and has reported a case of ventricular tachycardia with myocardial infarction involving the interventricular septum. Transient bundle branch block was observed between paroxysms. Two cases with autopsies have been recently reported in which the arrhythmia followed a lesion of the septum due to syphilis.[19]

Thus the relationship of disturbances of conduction and ventricular tachycardia has been suggested, but the importance of such defects of conduction in relation to other factors has not been shown, nor has the question of coincidence been eliminated.

Symptoms Associated with Ventricular Tachycardia.—Tachycardia per se may give rise to symptoms due to circulatory insufficiency. The site of these symptoms depends in the main on the relative degree of underlying arterial disease in various parts of the body. Cerebral manifestations (vertigo, fainting, temporary blindness, epileptiform seizures) have been reported by Barnes [20] and are presumably the result of cerebral anoxia. Only 1 of our patients is known to have had cerebral symptoms related to tachycardia. He lost consciousness at the onset of his attack.

The varying degrees of general circulatory collapse (shock) which occur with tachycardia are due primarily to the difficulty in maintaining an adequate cardiac output in the presence of the rapid rate and short diastolic pause. It has not proved practicable to analyze our cases with respect to the occurrence and degree of shock, although in several it was profound.

Patients may complain of pain or discomfort in the chest during an attack, although this is not a common symptom. Barnes and Willius [21] report 19 instances of precordial or substernal pain occurring in 380 cases of paroxysmal tachycardia of all types. The pain was described as aching or lancinating, and in some cases there was a sensation of constriction or oppression. Radiation to the arms occurred in a few

18. Miller, H.: Transitions Between Normal Intraventricular Conduction, Bundle Branch Block and Ventricular Tachycardia: Report of a Case, Am. Heart J. **19**:364, 1940.

19. Cossio, P.; Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia, Am. J. M. Sc. **194**:369, 1937. Coelho, E., and de Oliveira, A.: Syphilis of the Intraventricular Septum and Ventricular Tachycardia: Syphilis of the Pulmonary Artery, Arch. d. mal. du cœur **32**:17, 1939.

20. Barnes, A. R.: Cerebral Manifestations of Paroxysmal Tachycardia, Am. J. M. Sc. **171**:489, 1926.

21. Barnes, A. R., and Willius, F. A.: Cardiac Pain in Paroxysmal Tachycardia, Am. Heart J. **2**:490, 1926.

instances. In no case was there a history of typical anginal attacks between paroxysms of tachycardia. White [22] commented on the rarity of angina of effort in patients who have pain during a paroxysm of tachycardia but stated: "Finally, angina pectoris is induced in rare cases as a status anginosus by paroxysmal auricular fibrillation, paroxysmal auricular flutter, or tachycardia in patients who have already shown angina pectoris on effort."

It may be difficult or impossible to exclude myocardial infarction as a cause of pain during a paroxysm of ventricular tachycardia. Two of the patients in our series who complained of severe substernal pain during the paroxysm of tachycardia showed no clinical or laboratory evidence of myocardial infarction before or after, and there was no history of angina, although both showed cardiac enlargement and were diagnosed as arteriosclerotic heart disease. One of the patients in our series gave a definite history of angina pectoris, but did not complain of pain during the attack. Several patients were conscious of rapid cardiac action, which they described as palpitation or fluttering of the heart.

As has already been stated, in none of our cases have we proof that the onset of the tachycardia precipitated congestive heart failure, although in 2 a previously existent failure was aggravated. It is, however, well known that tachycardia of any type may produce congestive heart failure in a person with organic heart disease.

Clinical Diagnosis.—Any tachycardia, especially if it is paroxysmal, may be of ventricular origin, but it rarely is. If the patient has degenerative heart disease, and particularly if there is a myocardial infarction or a large overdose of digitalis, the likelihood of its existence is increased. As Levine [9] pointed out, one can on occasion make a presumptive diagnosis by direct examination if (1) the rhythm is rapid and essentially regular but slight irregularities can be detected; (2) the quality of the first heart sound varies in intensity in some of the cycles, or (3) attempts at "vagal" (carotid sinus) or ocular pressure prove ineffective in slowing the heart. None of these criteria is, however, constantly present or helpful. Many persons with ventricular tachycardia show no irregularity whatsoever. Variation in the first heart sound is a useful sign but depends on a varying relationship between auricular and ventricular contraction and hence is most helpful in cases with an independent auricular rhythm. It is not likely to occur when the auricles are fibrillating or if there is retrograde, ventriculoauricular conduction. Finally, although it is generally stated that ventricular tachycardia does not respond to vagal stimulation, often there is no such response in cases

22. White, P. D., and Camp, P. D.: The Status Anginosus Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia, Am. Heart J. **7**:581, 1931.

either of auricular tachycardia or of flutter; so this is by no means a clearcut differential point. Moreover, it is not impossible that on occasion such vagal stimulation may be effective in ventricular tachycardia. Although vagal stimulation did not stop the attacks in any case in the present series, we have recently observed 2 patients in whom the paroxysms were stopped by pressure on the carotid sinus (in 1 patient on two occasions). The cases of these patients fulfil most of the electrocardiographic criteria for paroxysmal ventricular tachycardia, since in both the ventricular complexes differed markedly from the QRS complexes in control records. Since auricular fibrillation was present in each case, an independent auricular rhythm could not be demonstrated. Because unfortunately the moment of onset or cessation of the attack was not recorded electrocardiographically, and because paroxysmal auricular flutter or even some other type of ectopic rhythm with aberrant ventricular response could not be unequivocally excluded, these cases have not been included in this series.

Prognosis.—It is difficult to estimate the importance of ventricular tachycardia in relation to mortality in most cases because of the severity of the underlying heart disease. Theoretically, rapid heart rate sustained for any length of time hastens myocardial exhaustion. This leads to increased ventricular irritability and raises the chances of ventricular fibrillation.

Various authors [23] have reported that the minute volume output of the heart during paroxysmal tachycardia is reduced by one tenth to two thirds of the normal output. One study of the blood gases during paroxysmal auricular tachycardia [24] showed a decrease in the degree of arterial oxygen saturation, a low oxygen saturation of venous blood and an increased coefficient of utilization.

Fall in blood pressure which sometimes accompanies paroxysmal tachycardia may also hinder the circulation. Tachycardia of any kind may precipitate or increase the severity of cardiac failure.[25] This was seen in at least 2 of our cases. The cerebral symptoms we described are probably related to decreased cardiac output and cerebral blood flow. It would seem at least possible, therefore, that in the presence of extensive heart disease prolonged tachycardia might be fatal. Few records have

23. Barcroft, J.; Bock, A. V., and Roughton, F. J.: Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, Heart **9**:7, 1921. Schöne, G.: The Magnitude of the Circulation in Paroxysmal Tachycardia, Klin. Wchnschr. **16**:804, 1937.

24. Carter, E. P., and Stewart, H. J.: Studies on the Blood Gases in a Case of Paroxysmal Tachycardia, Arch. Int. Med. **31**:390 (March) 1923.

25. Boyer, N. H.; Leach, C. E., and White, P. D.: Underlying Causes and Precipitating Factors of Congestive Heart Failure, in Blood, Heart and Circulation: Symposium, Publication 13, American Association for the Advancement of Science, 1940.

been taken on patients with ventricular tachycardia at the moment of death. However, these have shown that either ventricular fibrillation [26] or ventricular standstill [27] may be the terminal event.

Therapy.—As has been stated, simple measures such as pressure on the eyeball and pressure on the carotid sinus, which are often effective in auricular tachycardia, are rarely of benefit in the treatment of ventricular tachycardia. Digitalis is best omitted if it has been used before the attack. Moreover, because we believe that digitalis was a causal factor in some of our cases, we are doubtful of the wisdom of using it in the treatment of an attack even when no digitalis has been taken. Quinidine has been and still is widely used because of its depressant effect on ventricular conductivity. The use of quinine dihydrochloride intramuscularly has recently been reported.[28] Potassium chloride and magnesium sulfate have been used, but a definite evaluation of their worth is not yet possible. Both of these drugs have been tried in this hospital, with equivocal results with the former and negative results with the latter drug.

It is not possible to formulate a rigid set of rules governing dosage of quinidine, and the choice between the oral and the intravenous route is still a matter of opinion. The usual oral dose of 3 grains (0.19 Gm.) of quinidine sulfate as a test for sensitivity is advisable in every case. If the drug is to be given by mouth, it is best to plan a regimen of repeated doses at intervals of two or three hours, in view of the fact that its duration of action is brief and the situation is urgent. It is then possible to adjust the dosage to the response of the patient. Thus if 6 grains (0.39 Gm.) is given every two hours the total amount given at the end of twelve hours will be 36 grains (2.33 Gm.). If the tachycardia still persists the dosage can be increased, provided that no signs of toxicity have been observed. Levine and Stevens [29] stressed the necessity for adequate dosage and cited the case of a patient with ventricular tachycardia following myocardial infarction which proved refractory to treatment until the daily dosage reached 112 grains (7.24 Gm.). Daily doses up to 90

26. Thompson, I.: Ventricular Fibrillation Causing Sudden Death of a Patient with Disease of the Left Coronary Artery, J. A. M. A. **116**:2583 (June 7) 1941.

27. Miller,[18] Grieco, E. H., and Schwartz, S.: Observations on the Mechanism of the Dying Heart in a Patient with Ventricular Tachycardia, Am. Heart J. **16**:595, 1938.

28. Riseman, J. E. F., and Linenthal, H.: Paroxysmal Ventricular Tachycardia: Its Favorable Prognosis in the Absence of Acute Cardiac Damage and Its Treatment with Parenterally Administered Quinine Dihydrochloride, Am. Heart J. **22**:219, 1941.

29. Levine, S. A., and Stevens, W. B.: The Therapeutic Value of Quinidine in Coronary Thrombosis Complicated by Ventricular Tachycardia, Am. Heart J. **3**:253, 1927.

grains (5.82 Gm.) have been given repeatedly without untoward result. The necessity for early termination of the attack, especially in patients with extensive underlying heart disease, is obvious, but it must be remembered that the toxic effects of quinidine, such as severe vomiting and conduction disturbances, can be dangerous.

Very favorable results following intravenous administration of the drug have been reported but the danger of severe toxic reactions (vomiting, intraventricular block and standstill with unconsciousness and convulsions) is much greater. Strong and Munroe [30] reported success with intravenous administration of quinidine sulfate to a patient whose condition had been refractory to oral treatment. The attack was stopped only after continuous intravenous administration of 40 grains (2.59 Gm.) of quinidine sulfate in a 20 per cent solution, but the patient became unconscious and had an epileptiform convulsion at that point. Hepburn and Rykert [31] reported encouraging results with the intravenous method. In a series of 9 cases, in which 7 patients had had recent myocardial infarction, the attacks stopped in all, and 6 patients were alive for periods up to four years. Only 1 had a severe reaction while receiving quinidine. The results were much better than those obtained by the same authors in another group of 17 patients who did not receive quinidine intravenously, only 3 of whom lived longer than fifteen days. The analysis is not given in sufficient detail, however, to permit a definite conclusion. Hepburn and Rykert prepared a 12 per cent solution for intravenous use by dissolving 60 grains (3.88 Gm.) of quinidine sulfate in 500 cc. of sterile physiologic solution of sodium chloride or 5 per cent dextrose solution. The solution was then filtered and warmed and given at the rate of 100 to 120 cc., containing 12 to 14 grains (0.8 to 0.9 Gm.) of the drug, per hour. The average total dose was less than 20 grains (1.3 Gm.).

Quinidine was not administered intravenously to any of our patients, although quinine hydrochloride was so used in 1 instance with possible success. The difference between this drug and quinidine is thought to be mostly quantitative, the latter being about twice as strong as quinine hydrochloride.

Patients in whom quinidine given orally is ineffective or cannot be absorbed because of vomiting, and to whom it is considered inadvisable to administer the drug intravenously, may be treated by the intramuscular route. Since there is no preparation of quinidine at present

30. Strong, G. F., and Munroe, D. S.: Paroxysmal Ventricular Tachycardia, with Report of an Unusual Case, Am. Heart J. **19**:486, 1940.

31. Hepburn, J., and Rykert, H. E.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, Am. Heart J. **14**:620, 1937.

available for intramuscular use, quinine dihydrochloride may be used in dosages up to 7½ grains (0.5 Gm.), repeated if necessary at hourly intervals.

Kerr [32] stated that he seldom used quinidine in any form in ventricular tachycardia. He expressed the opinion that it is especially contraindicated in the presence of myocardial infarction, since "the conduction mechanism may be damaged and quinidine may further depress its activity, leading to ventricular fibrillation." Davis and Sprague [13] for the same reason suggested (in the treatment of any disorder) that quinidine be used with care in combination with digitalis in the presence of combined auriculoventricular and intraventricular block. It is probable that quinidine may itself occasionally precipitate ventricular tachycardia or fibrillation; theoretically, the chances of its doing so are increased when it is used in combination with digitalis or in the presence of disturbances of conduction. In 2 of the cases reported by Hepburn and Rykert,[31] ventricular tachycardia followed the treatment of auricular fibrillation by the oral administration of quinidine sulfate. This occurred in 1 of our cases, but the patient had received a large overdose of digitalis as well. Schwartz and Jezer [33] reported the precipitation of attacks of transitory ventricular fibrillation by both quinidine and quinine in 2 patients in whom the attacks also occurred spontaneously.

The theoretic objections on the ground that quinidine produces conduction disturbances and thus may prolong the attack or induce ventricular fibrillation are outweighed by the many reports attesting to its usefulness. Full appraisal of its value will necessarily be slow. Proved fatalities directly traceable to quinidine have been few, but that should not diminish care in the use of the drug. Repeated electrocardiograms are advisable, especially with intravenous injection, and if the latter method is used it is well to have frequent checks on the blood pressure.[30] It has proved impossible to draw definite conclusions from our series as to the value of quinidine therapy, and in general it is difficult to prove the usefulness of this drug by statistical evidence. In certain individual cases the value of quinidine or similar substances seems unquestioned. Even if the drug does not abolish the attack, a slowing of the ventricular rate often occurs and produces improvement in the circulation.

SUMMARY AND CONCLUSIONS

1. An analysis is reported of 36 cases of paroxysmal ventricular tachycardia. In 24 the electrocardiograms showed the attack to be uninterrupted, and in 12 the attacks occurred in short runs of tachycardia

32. Kerr, W. J.: Use of Quinidine in Cardiac Irregularities, in Stroud, W. D.: Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940.

33. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, Am. Heart J. **9**:792, 1934.

interposed between periods of normal supraventricular conduction. These two types have been arbitrarily designated as "persistent" and "intermittent" tachycardia.

2. In all but 1 case organic heart disease was present, in 28 cases being of the degenerative type.

3. Digitalis intoxication was clearly associated with the attack in 8 instances and was the probable precipitating factor in 9 more. One patient had received large doses of both digitalis and quinidine prior to the onset of the attack. Attacks occurred in association with myocardial infarction 6 times, and in 3 instances myocardial infarction was probably present.

4. Twenty-one patients died in the hospital, 8 in the attack and 12 (all but 1 of the remainder) within a month of its cessation.

5. The occurrence and prognosis of the attacks have also been analyzed in respect to associated electrocardiographic abnormalities and such factors as age, heart rate and width of QRS. The prognosis of paroxysmal ventricular tachycardia is serious, but it is essentially the prognosis of the underlying heart disease present. In our series the prognosis of the "intermittent" type was somewhat better than that of the "persistent" type.

6. The physiologic mechanism involved, the clinical symptomatology, the criteria for the clinical and electrocardiographic diagnosis and the therapy of the attacks with particular reference to quinidine are discussed.

STUDIES ON THE CLINICAL SIGNIFICANCE OF THE SERUM PROTEINS

II. THE RELATIONSHIP BETWEEN THE ALBUMIN-GLOBULIN RATIO, ALBUMIN, GLOBULIN AND TOTAL PROTEIN

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Denis [1] in 1856 was probably the first to report an investigation of the action of various salts on the separation of serum albumin from serum globulin. Hammerstein [2] in 1878 reported the utilization of the precipitating effect of salt for the quantitative estimation of the albumin and the globulin in horse and human serum. In 1882 Burckhardt [3] found that in starving dogs the albumin concentration of the serum fell while the globulin concentration remained stationary. In 1912 Epstein [4] reported that in 12 patients with "nephrosis" the only constant deviation from normal in the serum protein was the lowering of albumin. The absolute globulin level remained essentially constant. He expressed his findings as an albumin-globulin ratio ("A/G ratio"), and since his report this relative method of expression has become deeply rooted in medical literature. It should be noted, however, that when the albumin-globulin ratio is thus reversed, reporting this ratio alone, without reference to the total protein, often (as here) gives one the false impression of a change in the concentration of globulin.

Moore and Van Slyke [5] and others have shown that in certain conditions the albumin concentration of serum is lowered while the globulin concentration remains at a normal level and that therefore the total serum protein value falls in proportion to the drop in albumin concentration. On the other hand, Jeghers and Selesnick [6] found that

From the Johns Hopkins Hospital, Baltimore.

1. Denis, P. S.: Mémoire sur le sang, Paris, J. B. Baillière & fils, 1859; Nouvelles études chimiques, Paris, J. B. Baillière, 1856.

2. Hammerstein, O.: Ueber das Paraglobulin, Arch. f. d. ges. Physiol. **17**:413-468, 1878.

3. Burckhardt, A. E.: Beiträge zur Chemie und Physiologie des Blutserums, Arch. f. exper. Path. u. Pharmakol. **16**:322-343, 1882-1883.

4. Epstein, A. A.: A Contribution to the Study of the Chemistry of Blood Serum, J. Exper. Med. **16**:619-731, 1912.

5. Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis, J. Clin. Investigation **8**:337-355, 1930.

6. Jeghers, H., and Selesnick, S.: Hyperproteinemia: Its Significance, Internat. Clin. **3**:249-280, 1937.

an increase in total serum protein above normal was invariably due to an increase in serum globulin.

The present investigation was undertaken in order to clarify further the clinical significance of the relation between these two components of serum protein and to establish a more definite evaluation of the total serum protein. It is proposed also to determine the types of cases in which an accurate determination of serum albumin and serum globulin is informative and those in which it is not. It is hoped thus to eliminate wherever possible the laborious and difficult task of making accurate determinations of albumin and globulin and to show that in those cases in which such determinations are necessary the absolute values of albumin and globulin are essential and the albumin-globulin ratio alone misleading. In all other instances the determination of the total protein by a simple technic, such as the falling drop method,[7] suffices for clinical purposes.

MATERIAL AND METHOD

This report is based on 539 determinations of albumin and globulin on specimens of serum obtained from 345 patients in the Johns Hopkins Hospital over the period from November 1935 to September 1937. The data cover a great variety of diseases.

The method used was a macro-Kjeldahl modification of the Howe[8] procedure. The precipitation was done with sodium sulfate by the Howe technic, and the titrations were done with the methyl red–methylene blue indicator described by Johnson and Green.[9] Nonprotein nitrogen was determined by the micro-Kjeldahl method.

QUESTIONS RAISED BY THIS STUDY AND A REVIEW OF THE LITERATURE

A study of the material just mentioned as well as of the pertinent literature revealed the following interesting facts: 1. Decreases in total protein concentration below normal have been due almost invariably to decreases in albumin concentration. 2. Globulin concentration below the accepted normal level has been noted only in premature infants, in patients in the early period of severe hemorrhage and occasionally in

7. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: I. A Falling Drop Method for the Determination of Specific Gravity, J. Clin. Investigation **17**:369-372, 1938; II. The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, ibid. **17**:372-376, 1938; Studies on the Clinical Significance of the Serum Proteins: I. The Protein Content of Normal Human Venous and Capillary Serum and Factors Affecting the Accuracy of Its Determination, J. Lab. & Clin. Med. **27**:1457-1463, 1942.

8. Howe, P. E.: Use of Sodium Sulfate as Globulin Precipitant in Determination of Protein of Blood, J. Biol. Chem. **49**:93-107, 1921; The Determination of Protein in Blood: A Micromethod, ibid. **49**:109-113, 1921.

9. Johnson, A. H., and Green, J. R.: Modified Methyl Red and Sodium Alizarin Sulfonate Indicators, Indust. & Engin. Chem. **2**:2, 1930.

those with advanced cirrhosis. 3. Persistent increases in the total protein concentration above normal have, on the other hand, almost invariably been due to an increase in globulin concentration. 4. Increase in serum albumin content above normal has never previously been reported and seems not to occur except briefly in the early period of dehydration.

In recent years the marked chemical, physiologic and immunologic differences between albumin and globulin have become more clear: The globulin molecule is about two and a half times as large as the albumin. The osmotic influence of the albumin fraction is about four times that of the globulin fraction, and it is of greater importance in the maintenance of blood volume and fluid balance in the body. On the other hand, the immune bodies of the blood are principally in the globulin fraction. The albumin fraction is readily affected by the dietary intake of protein, but not the globulin. Globulin is much more quickly regenerated following hemorrhage than is albumin. It is likely, though not yet proved, that serum albumin is formed in the liver by synthesis from amino acids. Less is known of the origin of globulin, but it has been suggested recently by Bing and Plum [10] that the plasma cells of bone marrow and cells belonging to the reticuloendothelial system in and outside the marrow are of importance.

Many investigations have suggested that serum albumin and serum globulin must be considered separately in an evaluation of their clinical significance and that the albumin-globulin ratio alone is unsatisfactory. For example: in both nephrosis and venereal lymphogranuloma the albumin-globulin ratio is reversed; however, in the former this is due to a lowering of the serum albumin, and in the latter it is due to an increase in serum globulin.

We are therefore faced with two problems: 1. Is it sufficient to give only the figure for the total protein; and if so, in which cases should this be done? 2. In those cases in which the figure for total protein alone is not sufficient, is it advisable to give the albumin-globulin ratio or would it be clearer and would the determinations be more valuable if the absolute values of the albumin and globulin fractions were presented?

ANALYSIS OF DATA

The data represent such a variety of cases as would ordinarily be seen in a large, busy hospital over a two year period. For purposes of study, they fall naturally into two main divisions. The first division consists of cases in which the concentration of the total serum protein was normal or below normal (7.5 Gm. per hundred cubic centimeters

10. Bing, J., and Plum, P.: Serum Proteins in Leucopenia, Acta med. Scandinav. **92**:415-428, 1937.

or less) and constitutes 91 per cent of all the cases studied; the second division consists of cases in which there was associated hyperproteinemia (total serum protein above 7.5 Gm. per hundred cubic centimeters) and constitutes only 9 per cent of the cases studied.

Cases in Which Total Protein Was 7.5 Gm. or Less per Hundred Cubic Centimeters.—In 71 per cent of all the cases in which the concentration of the total serum protein was found to be 7.5 Gm. or less per hundred cubic centimeters, only albumin was affected. In 29 per cent both albumin and globulin were changed.

First consideration will be given the larger group—that in which only albumin was affected. In this group globulin remained within normal limits, and a linear relationship was found to exist between total protein and albumin. By application of the method of least squares to the data of this group, the following equation was determined:

$$A = 0.93 \times (TP - 2.1)$$

in which *A* represents albumin and *TP* total protein. The coefficient of correlation (*r*) is 0.9967, and the standard error of estimate is $\pm$ 0.4 Gm. per hundred cubic centimeters.

Thus it can be seen that in this first group (71 per cent of the cases in this division) the concentration of albumin can be predicated from that of total protein with a standard error of estimate of less than 10 per cent; in other words, the total protein alone gives sufficient indication for clinical purposes.

The smaller group, in which both albumin and globulin were affected, includes all forms of hepatic disease, whether carcinoma, primary or metastatic, or cirrhosis, primary or secondary to chronic heart failure. It also includes the simultaneous occurrence of two conditions, the one causing hyperglobulinemia, the other hypoalbuminemia—such as syphilis and nephritis, tuberculosis and malnutrition, or venereal lymphogranuloma and diarrhea. Of the nephritides, only acute glomerular nephritis is at all regularly associated with decreased albumin and increased globulin. Here the nephritis probably accounts for the decrease in albumin and the associated infection for the increase in globulin. In all of the types of cases just cited, globulin is increased and albumin decreased. Both albumin and globulin may be decreased below normal in the early stage of severe hemorrhage or in far advanced cirrhosis. It is evident, therefore, that in the conditions which make up this entire group the values of albumin and globulin must be considered individually.

In these conditions globulin varies so much that no linear correlation between albumin and total protein obtains, and obviously there is no correlation between total protein and globulin since albumin varies so much.

The correlation equation for the data of this group is $A = 0.42 \times (TP + 0.34)$. The coefficient of correlation is 0.4319, and the standard error of estimate is $\pm$ 0.7 Gm. per hundred cubic centimeters, or 24 per cent.

The accompanying table gives an analysis of these data. Briefly, 42 per cent of the cases in this group were instances of hepatic involvement; 29 per cent, acute glomerular nephritis with its usual associated infections; 26 per cent, two conditions occurring simultaneously, the one affecting albumin and the other globulin. In 3 per cent, not included in the table, there was severe acute hemorrhage, and in this small group albumin was lowered and globulin also was slightly below normal during the early period of the hemorrhage. In this type of case the con-

Conditions Causing Hyperglobulinemia and Hypoalbuminemia Simultaneously

1. Hepatic diseases
   - A. Cirrhosis
     - (*a*) Primary
     - (*b*) Secondary to heart failure
   - B. Carcinoma
     - (*a*) Primary
     - (*b*) Metastatic
2. Acute glomerular nephritis
3. Combination of two diseases, the one causing an increase of globulin and the other a decrease of albumin, as for example

A. Increase of gobulin	B. Decrease of albumin
(*a*) Syphilis	(*a*) Nephritis
(*b*) Tuberculosis	(*b*) Malnutrition
(*c*) Venereal lymphogranuloma	(*c*) Diarrhea
(*d*) Periarteritis nodosa	
(*e*) Subacute bacterial endocarditis	
(*f*) Multiple myeloma	

centration of globulin returns to normal quickly, and thereafter changes in total serum protein are related to changes in albumin in a linear fashion, as noted in the first formula given.

Cases in Which Total Protein Was Above 7.5 Gm. per Hundred Cubic Centimeters.—Total serum protein was above 7.5 Gm. per hundred cubic centimeters in 9 per cent of the 345 cases studied. In each instance the increase was due to an increase in globulin. This finding and a review of the data in the literature show that total serum protein above 7.5 Gm. per hundred cubic centimeters means almost invariably an increase in globulin above normal, a fact which suffices for most clinical purposes. In the majority of cases in which hyperproteinemia occurred there was slight lowering of the apparently more easily affected albumin fraction. Of course, when it is important to know the exact level of albumin in this group of cases, it is necessary to determine it quantitatively. This group of cases will be discussed in more detail in a subsequent paper.

The Albumin-Globulin Ratio.—In each of the three groups considered, a certain percentage of the determinations showed a reversed albumin-globulin ratio, 18 per cent in the first group, 54 per cent in the second and 59 per cent in the third. The reversal occurred so frequently that it did not serve to distinguish any particular pathologic entity from any other in which serum proteins were affected. In the first group of cases the ratio was reversed because albumin was lowered—even though globulin was normal. In the second group of cases it was reversed because albumin was lowered and globulin increased. In the third group of cases it was reversed because globulin was so markedly increased that reversal occurred even though albumin was normal or only slightly decreased. It is obvious, therefore, that one can make no practical application of the albumin-globulin ratio without reference to the total protein. Since, then, the significance of the albumin-globulin ratio depends solely on its inference of the absolute values of albumin and globulin, it would be much simpler and more conclusive to refer directly to the absolute values for total serum albumin and total serum globulin.

COMMENT

This study suggests that a good procedure for a busy clinical laboratory would be first to determine the total serum protein routinely by a simple, rapid and reliable technic, such as the falling drop method.[7] In the majority of cases the clinician can obtain from this all the information he requires. If, however, the total protein is within the normal limits and the clinician suspects a condition or conditions in which both albumin and globulin may be affected, as discussed (see table), then an accurate determination of the absolute values of albumin and globulin should be done by a reliable technic, such as the Kjeldahl. If the latter cannot be used, the formaldehyde-gel test and the globulin precipitation test are simple and are said to indicate any increase in globulin.[11]

11. Recommended technics are as follows: For the formaldehyde-gel test (Bing, J.: The Formolgel Reaction and Other Globulin Reactions, Acta med. Scandinav. **91**:336-356, 1937) add 2 drops of 40 per cent solution of formaldehyde to 1 cc. of serum and read after three hours' standing at room temperature. If the tube can be inverted without losing its contents, the test is positive. For the globulin precipitation test (Naumann, H. N.: Saturation of Serum with CO_2: A Simple Test for Hyperglobulinemia, Proc. Soc. Exper. Biol. & Med. **39**:377-380, 1938) add 0.1 cc. of serum to 1.0 cc. of distilled water in a test tube 10 mm. wide. Saturate with alveolar air and read after fifteen minutes. If definite cloudiness appears, the concentration of globulin is said to be more than 3.0 Gm. per hundred cubic centimeters.

The falling drop principle has been applied for the determination of albumin and globulin, but the necessary precautions are too rigorous for routine use, and since only 27 determinations have been correlated with the results obtained by Kjeldahl technic, this method cannot be recommended at this time. (Barbour, P. H., Jr.: The Application of the Falling-Drop Method for Specific Gravity Measurement to the Determination of Serum Albumin, Yale J. Biol. & Med. **14**:107-114, 1941).

Thorough application of this procedure instead of the more usual method of determining albumin and globulin by the relatively inaccurate colorimetric method would enhance the value of serum protein determinations and make it possible to do more of them.

SUMMARY

The expression of the albumin-globulin ratio without reference to the total serum protein content is misleading and should be discarded. The absolute values for albumin and globulin should be used for more clarity.

In all cases in which the total serum protein content is below 7.5 Gm. per hundred cubic centimeters and the patient is known not to be suffering from one of the conditions mentioned in the accompanying table, the albumin level of the serum may be predicted from the total protein level by the formula $A = 0.93 \times (TP - 2.1)$ with sufficient accuracy for ordinary clinical purposes.

When the concentration of total serum protein is above 7.5 Gm. per hundred cubic centimeters, it may safely be assumed that the increase is due to a rise in globulin, but the degree of this rise cannot be predicted. The fact that globulin is increased in any particular case may be helpful in differential diagnosis. Further, it may be helpful to know whether this increase is large or small; otherwise the degree of change in globulin is not helpful in the same sense that the degree of change in albumin is. In view of this, simple tests for the detection of hyperglobulinemia are suggested for most clinical purposes.

In the conditions listed in the table a change in the concentration of total serum protein has no quantitative significance. Here too, however, a concentration below 6.0 Gm. per hundred cubic centimeters means a decrease in albumin (although this indicates the amount of decrease only relatively) and a concentration above 7.5 Gm. per hundred cubic centimeters indicates an increase in globulin. A normal concentration of total protein (6.0 to 7.5 Gm. per hundred cubic centimeters) in this group may be due to a decrease in albumin and an increase in globulin. It is for this group that there is the greatest need for an accurate, simple and rapid method of determining serum albumin and globulin. The most reliable practical technic at the present time remains the Kjeldahl. For rapid results a combination of the falling drop technic with the simple formaldehyde-gel or the globulin precipitation test may also be used here.

If these facts are borne in mind, the much overworked diagnostic laboratories can be spared considerable time, and a clearer interpretation of serum proteins can be obtained.

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SICKLE CELL ANEMIA IN THE WHITE RACE

WITH REPORT OF CASES IN TWO FAMILIES

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In view of the rarity of sickle cell anemia in the white race, 2 cases of this disease in an active form in white families are here presented.

REPORT OF CASES

CASE 1.—Gladys C. (fig. 1), a 9 year old white school girl born of Spanish parentage in New Orleans, came to the outpatient department of the Charity Hospital on May 29, 1939, complaining of pain in the throat. Her tonsils were slightly enlarged and inflamed. Her mother stated that the child often had "head and chest colds" and appeared to be weaker than other children.

She had been delivered normally at term and had weighed 7 pounds (3,175 Gm.). On the second day after birth a deep yellow discoloration appeared all over her body. At the age of 3 weeks she was shown to a doctor, who advised the mother not to pay any attention to this condition. At the age of 5 years she had a severe attack of measles.

On Oct. 10, 1939, when she again came to the clinic, she appeared deeply jaundiced. According to her parents she had had a yellow discoloration of the whole body all her life. At times it became deeper and at times lighter, but it never disappeared completely. Her scleras had a greenish yellow tint. She was subject to repeated attacks of "sore throat." For the past two years such attacks had been increasing in intensity. She was confined to bed six times during this period and finally had to abandon her studies. Occasionally she had some abdominal discomfort accompanied by diarrhea, but without nausea or vomiting. There was no history of pains in muscles or joints.

Family History.—Gladys' father and mother were both of Spanish descent and came from Nicaragua to New Orleans, where they had resided for twenty-five years.

The father (fig. 2) a 42 year old common laborer, was in good health, and his blood picture was normal. A moist preparation of his whole blood did not show any abnormality in forty-eight hours. The mother (fig. 2), a 38 year old factory worker, was slightly anemic and had suffered from "menstrual irregularities" for years. Examination of a direct smear revealed no abnormalities in the blood, but in a moist preparation of her whole blood after forty-eight hours 89 per cent of the erythrocytes became sickled.

A maternal aunt of the patient died at the age of fourteen. Before her death she "turned completely yellow." A paternal aunt of the patient, Victoria C. (fig. 2), aged 16, was a school girl in good health. Her blood picture, like

From the Department of Pathology and Bacteriology, Louisiana State University Medical Center, and the Charity Hospital of Louisiana, New Orleans, and the Department of Pathology, Passaic General Hospital.

Fig. 1.—Gladys C. (case 1).

Fig. 2.—Gladys' family.

that of her brother (the father of the patient), was normal both in a direct smear and in a moist preparation after forty-eight hours.

The paternal grandfather of the patient died at the age of 73 of rheumatic fever. The paternal grandmother of the patient was 65 and in good health. The paternal great-grandparents, about whose health the patient's father could not give any definite information, came from Spain. The maternal grandparents of the patient had resided all their lives in Nicaragua. The maternal grandmother died at the age of 35. The history of her illness, as related by her daughter, the mother of the patient, is suggestive of active sickle cell anemia. The maternal grandfather was 83 and in good health. The maternal great-grandparents came to Nicaragua from Spain.

The sister of the patient, Mercedes C. (fig. 2), a 5 year old school girl, appeared to be normal, though slightly undernourished. She had measles at 3. Examination of a direct smear did not reveal any abnormality in the blood. However, after forty-eight hours 81 per cent of the erythrocytes in a moist preparation became sickled. The brother of the patient, Louis C. Jr. (fig. 2), a 7 year old school boy, was slightly anemic. His conjunctivas and labial mucosae were pale, and he was of delicate build. He had had measles at the age of 4 and suffered from occasional headaches and nasal bleedings. His blood picture indicated a slight anemia of normocytic hypochromic type. In a moist preparation of his whole blood 93 per cent of the erythrocytes became sickled after forty-eight hours. In spite of the presence of anemia and sickle-emia in this boy the clinicopathologic complex of the active sickling trait was absent.

Physical Examination.—Gladys was a poorly nourished, slender white girl weighing 48 pounds (21.8 Kg.) (average weight 64 pounds [29.0 Kg.]) and 4 feet (121.92 cm.) tall (average 4 feet 4 inches [132.08 cm.]).[1] The temperature was 99.8 F., the pulse rate 96 and the respiratory rate 20. She appeared to be sufficiently intelligent for her age. No abnormalities were found in her lungs. The heart was slightly enlarged; its right border extended 1 cm. to the right of the right parasternal line. The apex beat was in the fifth intercostal space by the left mamillary line. A loud systolic murmur of hemic origin was especially audible at the aortic and mitral valves. The upper and lower extremities were normal; there were no ulcers and no traces of the old, healed scars. The spleen was not felt on palpation and was found to be small on deep percussion. The liver was enlarged; its lower border extended 6 cm. below the right costo-chondral line and was 2 cm. above the umbilicus. The gallbladder was not sensitive to pressure, and there was no evidence of general or local lymphadenopathy. Reflexes and systems did not show any noticeable abnormality.

Laboratory Data.—There were 2,688,000 red blood cells, 11,500 white blood cells and 948,000 platelets per cubic millimeter of blood. The hemoglobin concentration was 49 per cent (7.1 Gm. per hundred cubic centimeters), on the 14.5 Gm. = 100 Sahli scale. Hematocrit readings showed 22 volumes per cent of packed erythrocytes. The mean corpuscular volume was 81.5 cubic microns and the mean corpuscular hemoglobin 26.3 micromicrograms. The mean corpuscular hemoglobin concentration was 32.3 per cent, the color index 0.9 and the icterus index 25. The van den Bergh reaction indicated 5.25 units of bilirubin in the

1. The Average Weight and Height of Children, Tables of the National Child Health Council, cited in De Re Medicina, Indianapolis, Eli Lilly & Company, 1941, p. 298.

blood serum. The fragility test showed hemolysis beginning at a 0.34 per cent concentration of sodium chloride and complete at a 0.26 per cent concentration. The coagulation time was four minutes and the bleeding time five minutes.

Examination of a direct blood smear (by my own method) [2] revealed 41 per cent neutrophils, 8 per cent eosinophils, 1 per cent basophils, 42 per cent lymphocytes and 8 per cent monocytes. Occasional fragile cells (degenerated leukocytes) were found (fig. 4). The Schilling hemogram indicated a slight regenerative shift to the left, with 2 per cent myelocytes, 4 per cent metamyelocytes, 10 per cent band forms and 25 per cent segmented forms among the neutrophils.

In a vital staining preparation of 400 leukocytes and 10,000 erythrocytes, 3 per cent normoblasts and 27.5 per cent reticulocytes were encountered and marked basophilic stippling and polychromatophilia were observed. Although

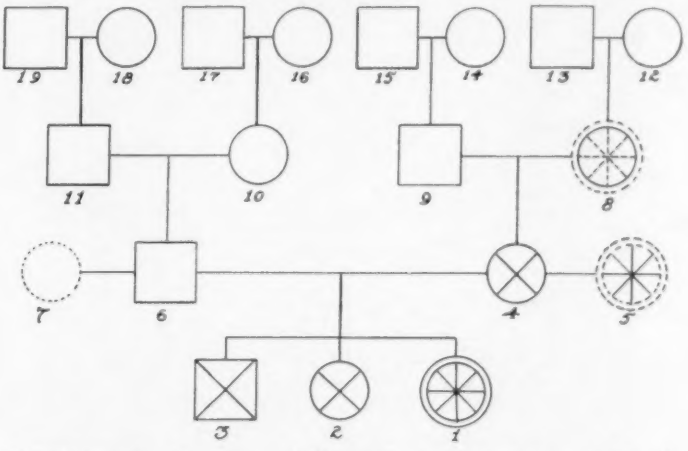

Fig. 3 (chart 1).—Family tree of Gladys C. *1.* Gladys C., 9 year old patient. Sickle cell anemia, active. *2.* Mercedes C., 5 year old sister of the patient. Sicklemia. *3.* Louis C., Jr., 7 year old brother of the patient. Sicklemia and anemia. Possibly subclinical type of sickle cell anemia. *4.* Mrs. Louis C., 38 year old mother of the patient. Sicklemia. *5.* Maternal aunt of the patient. Died at the age of 14. The history given is suggestive of sickle cell anemia, active. *6.* Louis C. Sr., 42 year old father of the patient. No blood dyscrasia found. *7.* Victoria C., 16 year old paternal aunt of the patient. No blood dyscrasia found. *8.* Maternal grandmother of the patient. Died at the age of 35. The history given is suggestive of sickle cell anemia, active. *9, 12, 13, 14 and 15.* Maternal ancestors of the patient. *10, 11, 16, 17, 18 and 19.* Paternal ancestors of the patient.

about one third of the erythrocytes appeared to be hypochromic, many of them, especially those having sickle and oat shapes, contained an increased amount of

2. Ogden, M. A.: A New Method of Making Smears for Hematologic, Cytologic and Bacteriologic Examinations, Am. J. Clin. Path. (Tech. Supp.) **3**:183, 1939.

hemoglobin. There were 19 per cent of sickled cells, 6 per cent of oat cells, 3 per cent of ovalocytes and 1.2 per cent of elongated erythrocytes. The remaining erythrocytes were unicornate, polycornate, filiform, monocaudate and bicaudate (caudocytes). There were also some with sharp ends at one or both poles (spiculocytes) and others of indefinite form, some of which were only artefacts.

After production of local anoxemia (by the method of Scriver and Waugh [3]) examination of a moist preparation of the whole blood by Emmel's method [4] revealed 6.5 per cent of erythrocytes which sickled immediately. Eight per cent had sickled in fifteen minutes, 12 per cent in half an hour, 17 per cent in one hour, 40 per cent in two hours, 55 per cent in three hours, 73 per cent in six

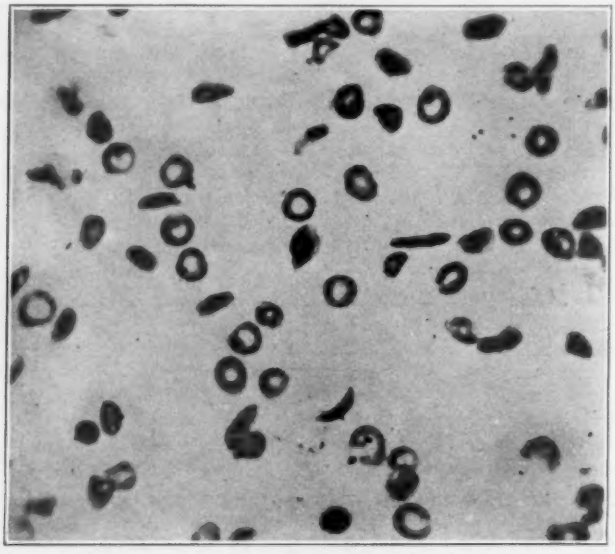

Fig. 4.—Direct smear of the peripheral blood, Gladys C. Drepanoblast and several drepanocytes are observed.

hours, 95 per cent in twenty-four hours and 99 per cent in forty-eight hours. The blood was kept at room temperature.

The blood picture was indicative of severe sickle cell anemia in the active stage and was characterized by leukocytosis, 1 plus, with a slight regenerative shift to the left, erythropenia, 2 plus, with a moderate erythrogenesis, 2 plus, and moderate eosinophilia compatible with sickle cell anemia.

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3. Scriver, J. B., and Waugh, T. R.: Studies on a Case of Sickle-Cell Anemia, Canad. M. A. J. **23**:375, 1930.

4. Emmel, V. E.: A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**: 586 (Oct.) 1917.

The urine was clear, gave an acid reaction and had a specific gravity of 1.020. Dextrose was not found; 0.01 per cent of albumin was present, and the reaction for urobilin was positive in a dilution of 1:100. Microscopic examination after centrifugation for five minutes at 500 revolutions per minute revealed 5 to 8 leukocytes per high power field and occasional mucous threads and epithelial cells, but no casts or erythrocytes.

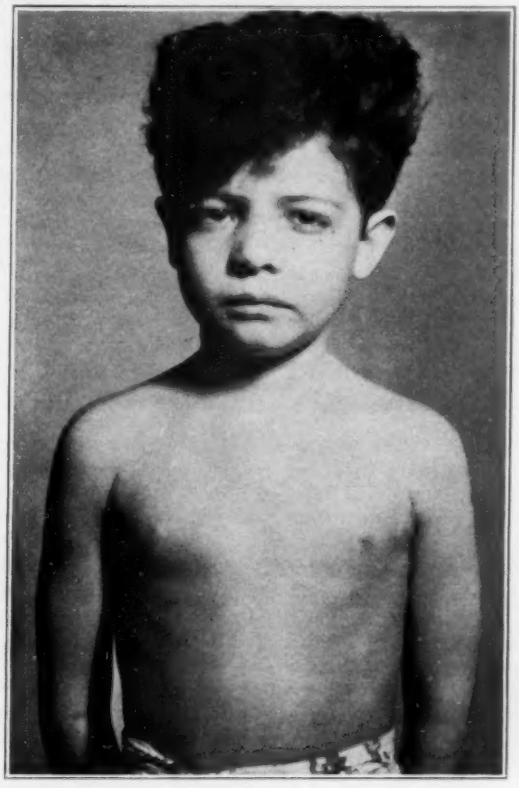

Fig. 5.—Johnny M. (case 2).

Examination of the stool when the patient was on a meat-free diet revealed occult blood (1 plus). Examination of a direct smear, a centrifugal concentration specimen and a zinc sulfate flotation specimen did not reveal any evidence of ova, cysts or parasites.

CASE 2.—Johnny M. (fig. 5), an 8 year old white school boy born in Passaic, N. J., was admitted to the Passaic General Hospital on March 19, 1941 for treatment of "rheumatic fever." He was of German extraction on the paternal side and of mixed Indian (?) and Scotch (?) extraction on the maternal

side.[5] His mother stated that although he was a full term baby he weighed only 5 pounds (2,268 Gm.) at birth, in contrast to her other children, whose average birth weight was 7 pounds (3,175 Gm.). In his early childhood he suffered from chickenpox, pertussis and frequent colds. Tonsillectomy was performed when he was 3 years old. He was always a "sickly" child and suffered from repeated and rather severe "nosebleeds." He went to school, but was compelled by ill health to leave it frequently. According to his teacher, he showed little progress in his studies and was considered to be below the average level. For the past two years he had suffered from rather severe pains in muscles and joints, especially in the lower extremities. These pains were often accompanied by fever. He was treated by his family physician for "rheumatic fever." Exposure to ultraviolet radiation and other physical therapeutic procedures were used without success.

Physical Examination.—At the time Johnny entered the hospital he was a pale, anemic-looking, slightly jaundiced, undernourished white child. He was so distinctly underdeveloped that no one considered him to be older than 4 years. He weighed 37 pounds (16.8 Kg.) (average normal, 58 pounds [26.3 Kg.]), and his height was 43 inches (109 cm.) (average normal, 50 inches [127 cm.]).

His temperature on admission was 99.8 F., and during his stay in the hospital it showed variations from 98.5 F. to 101.4 F. (mainly evening elevations). The temperature curve was of the continuous irregular type. His pulse rate varied from 80 to 115 and his respiratory rate from 20 to 30.

The heart was slightly enlarged; its right border extended 0.5 cm. to the right from the right parasternal line. A dull systolic murmur of hemic origin was noted.

No ulcers or old scars were found either on the upper or on the lower extremities. The spleen was not enlarged. The liver was moderately enlarged, its lower border being 4 cm. below the right costochondral line. The gallbladder was not sensitive to pressure, and no general or local adenopathy was noted.

Both knee and ankle joints were painful on moderate pressure, but were not swollen. The muscles of both femoral regions were similarly affected.

With the aid of roentgenograms slight cardiac hypertrophy was demonstrated. Roentgengrams of the skull, arms and legs failed to reveal any evidence of destructive or productive changes in the bones. Masses in the mediastinum and active pulmonary lesions could not be demonstrated by means of roentgenograms. Reflexes and systems did not show obvious deviation from normal conditions.

Laboratory Data.—The number of red blood cells showed variations from 2,870,000 to 4,490,000 (after blood transfusions), with a hemoglobin concentration of from 45 per cent (6.52 Gm.) to 58 per cent (8.41 Gm.), on the 13.8 Gm. = 100 per cent Sahli scale. The number of white blood cells varied from 11,600 to 11,800. Examination of a direct blood smear revealed 71 per cent neutrophils (Schilling hemogram: 2 per cent metamyelocytes, 7 per cent band forms, 62 per cent segmented), 5 per cent eosinophils, 1 per cent basophils, 17

5. For a long time Johnny's mother attempted to conceal her Negro ancestry by making confusing statements concerning the Indian and Scotch ancestry, which apparently constituted only minor branches in her family tree, as is indicated in figure 8. She finally admitted Negro ancestry.

per cent lymphocytes and 6 per cent monocytes. Among the erythrocytes (fig. 6) there were 8 per cent sickle cells, 6 per cent oat cells and occasional cylindrocytes and ovalocytes. In a moist preparation of whole blood 7 per cent of the red blood cells were sickled within fifteen minutes, 36 per cent within fifteen hours and 99 per cent within twenty-four hours.

The sedimentation rate of the red blood cells on March 22, 1941 was one hundred and seventy minutes (Linzenmeier's method). The reaction to the Kahn test of the blood was negative. Examination of culture material from the throat did not reveal diphtheria bacilli or other pathogens.

A specimen of urine taken March 20, 1941 was clear and light amber. The reaction was alkaline and the specific gravity, 1.005. Dextrose and albumin were not found. The reaction for urobilin was positive in a dilution of 1 : 50. Microscopic examination of the centrifuged sediment revealed occasional degenerated

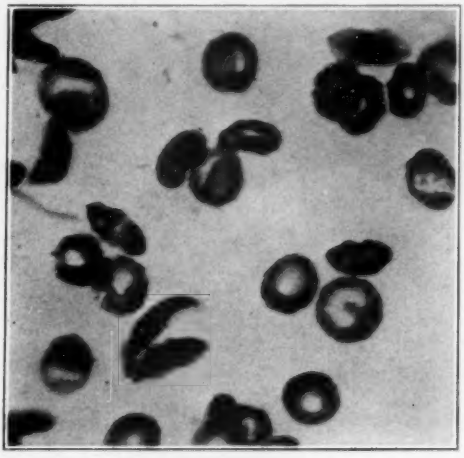

Fig. 6.—Direct smear of the peripheral blood, Johnny M.

leukocytes and epithelial cells of urinary bladder type, amorphous phosphate, 1 plus, and occasional triple phosphate crystals.

The electrocardiogram showed slight deviation of the axis to the left.

The diagnosis was active sickle cell anemia.

Family History.—Johnny's father (fig. 7), a 40 year old electrician, was born in the Panama Canal Zone and had always been in good health. His blood picture was normal and the erythrocytes in a moist preparation did not show any abnormality after forty-eight hours. Johnny's mother (fig. 7), a 34 year old housewife, was born in Buffalo. She was slightly anemic. The red blood cell count was 3,600,000, the hemoglobin concentration 66 per cent (9.1 Gm.), and the white blood cell count 5,100. Examination of a direct smear of her blood did not reveal any noticeable abnormality of the erythrocytic structure except slight anisocytosis. In a moist preparation of the blood 76 per cent of the erythrocytes became sickled within twenty-four hours.

Johnny's eldest brother, Ernest (fig. 7), aged 14, had had in childhood an attack of poliomyelitis, which, however, did not cripple him. The red blood

cell count was 4,800,000, the hemoglobin concentration 78 per cent (10.76 Gm.) and the white cell count 9,200. Examination of a direct blood smear revealed no abnormal erythrocytic structure. In a moist preparation of the whole blood 88 per cent of the red blood cells became sickled within a twenty-four hour period. Joseph (fig. 7), aged 10, another brother of Johnny, had a red cell count of 4,550,000, a hemoglobin concentration of 84 per cent (11.59 Gm.) and a white

Fig. 7.—Johnny's family.

cell count of 6,900. Examination of a direct smear of his whole blood revealed no abnormal erythrocytic structure. Ninety-two per cent of the erythrocytes in a moist preparation of whole blood became sickled within twenty-four hours. Joyce (fig. 7), Johnny's baby sister, 19 months old, had a red cell count of 3,900,000 and a hemoglobin concentration of 50 per cent (6.9 Gm.). Examination of a direct smear revealed slight anisocytosis. In a moist preparation of the whole blood 63 per cent of the erythrocytes became sickled within twenty-four hours.

Johnny's maternal grandmother, aged 55, had a red cell count of 4,050,000, a hemoglobin concentration of 78 per cent (10.76 Gm.) and a white cell count of 8,800 (fig. 8). Neither a direct smear nor a moist preparation of the whole blood showed any abnormal erythrocytic morphology. Johnny's maternal aunt, aged 31, did not show any abnormal erythrocytic morphology either in a direct smear or in a moist preparation after a routine forty-eight hour check.

A paternal great-grandfather and a paternal great-grandmother of Johnny were Germans. A paternal great-great-grandfather was of pure German descent. A paternal great-great-grandmother was of mixed German and English extraction. The maternal grandfather died at the age of 24 of "some heart trouble," according to Johnny's maternal grandmother, who was still living with the family. A maternal great-grandmother lived in Charleston, S. C. She was of "half Indian (?)" blood. She died at the age of 80 of "indigestion." Her husband (a maternal great-grandfather of Johnny), who died of "dropsy" (?) at the age of

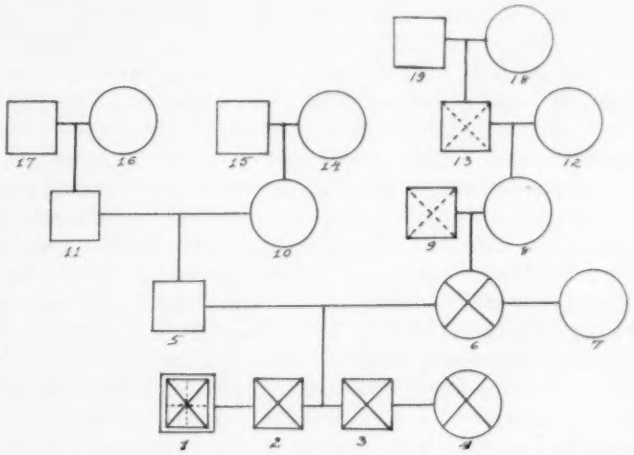

Fig. 8 (chart 2).—Family tree of Johnny M. *1.* Johnny M., 8 year old white boy. Sickle cell anemia, active. *2.* Ernest M. Jr., 14 year old brother of Johnny. Sicklemia. *3.* Joseph M., 10 year old brother of Johnny. Sicklemia. *4.* Joyce M., 19 month old sister of Johnny. Sicklemia. *5.* Ernest M., 40 year old father of Johnny. No blood dyscrasia found. *6.* Mrs. Ernest M., 34 year old mother of Johnny. Sicklemia. *7.* Mrs. E. E., 31 year old maternal aunt of Johnny. No blood dyscrasia found. *8.* Mrs. E. P., 55 year old maternal grandmother of Johnny. No blood dyscrasia found. *9.* Maternal grandfather of Johnny. Died at the age of 24. The history is suggestive of active sickle cell anemia. *13.* Johnny's maternal great-grandfather, who died at the age of 28 was a Mulatto (! ! !). *19.* The maternal great-great-grandfather of Johnny was a Negro (sic ! ! !). *12* and *18.* Maternal ancestors of Johnny. *10, 11, 14. 15, 16* and *17.* Paternal ancestors of Johnny.

28, was a mulatto. His father (a maternal great-great-grandfather of Johnny) was a Negro. His mother (a maternal great-great-grandmother of Johnny) was of "mixed" Negro and white blood.

Blood Grouping of Johnny's Family.—Johnny's father belongs to group A, and his mother to group O. Johnny and his two brothers all belong to group A.

It is interesting that although in this family the mother transferred the sicklemic trait to all her children, they inherited the father's blood group containing agglutinogen A. The most remarkable fact from the anthropologic standpoint is that Johnny scarcely shows any characteristics of the Negro race. His mother has crisp, curly hair and a rather wide, flat nose, thus showing some resemblance to a Negress, although her skin is rather light (fig. 7).

INVESTIGATION

In this work the manifestations of the sickling trait were classified as sickle cell anemia and sicklemia. The latter was considered to be of two varieties, immediate and delayed, between which no sharp line can be drawn. Sickle cell anemia, an active sickling trait, was defined as a clinicopathologic entity in which sickling of the erythrocytes in a moist preparation takes place either immediately or within a short interval, so that at the end of six hours at least 15 per cent of the erythrocytes are sickled. The presence of sickle or oat cells in varying numbers may also be observed in the direct smear.

The phenomenon of sickling is accompanied by a definite clinicopathologic complex, which, according to the general consensus, has numerous manifestations, including jaundice, hepatomegaly, splenomegaly (or splenic atrophy), severe anemia, urobilinuria, ulcers of the legs, abdominal crises, superficial, regional or generalized lymphadenopathy, arthritic and muscular pains, fever, heart murmurs, thickening of the skull, especially of the parietal bones, osteoporosis and osteosclerosis, especially in the long bones, delayed physical development, weakness and sometimes mongoloid facial features. This familial and hereditary disease is transferred to the offspring according to mendelian law (as Sydenstricker [6] first pointed out). It is of extremely chronic character, and may, as in this case, be of lifetime duration with periods of exacerbation and remission. At some periods and in some patients many symptoms may be absent, but the most constant, I believe, are jaundice (clinical or subclinical) and hepatomegaly in combination with the characteristic blood picture already described.

Immediate sicklemia is characterized by the sickling, immediately or within a short period of time (less than six hours), of over 15 per cent of the erythrocytes in the moist preparation. In the direct smear a few sickle or oat cells may sometimes be observed. This condition may also be accompanied by anemia, but the whole clinicopathologic complex of sickle cell anemia, just described, may be absent.

In delayed sicklemia examination of a direct smear does not reveal any characteristic picture. Sickling of the erythrocytes develops in the moist preparation only after prolonged standing. In some cases in this

6. Sydenstricker, V. P.: Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12 (July 5) 1924.

series only occasional cells became sickled at the end of twenty-four hours. However, at the end of forty-eight hours as many as 23 to 38 per cent of erythrocytes became sickled. The moist preparations were observed for at least forty-eight hours, since if the period of observation is limited to twenty-four hours delayed sicklemia may be missed.

I refer to sicklemia as "immediate" or "delayed" without the use of the word "latent," because although in such patients the typical clinicopathologic complex of the active form is not found, there apparently exists a variety of subclinical types of sickle cell anemia which may be activated or abated by factors not yet well understood. The speed of sickling may be an index of activity of trait only in some cases.

I do not believe that the present state of knowledge of this disease permits any attempt at satisfactory classification. The present study suggests that the sicklemic trait is acquired prenatally and that by the time of birth it appears either in the active form, sickle cell anemia, or in the inactive, sicklemia. In this series I was unable to find a single case of "possible activation" of the sickling trait.

The forms noted in this series were: active sickle cell anemia (in the stage of relapse or remission), sicklemia in the subclinical, symptomless stage and sicklemia without severe anemia but with only a few symptoms of the active trait. Whether persons born of sicklemic parents and themselves not showing any sickling trait are capable of producing sicklemic progeny is not yet definitely established. For the purpose of determining the incidence of the sickling trait in the white and Negro races in New Orleans, I studied 1,602 unselected, consecutive cases in the outpatient department of the Charity Hospital at New Orleans from Nov. 7, 1939 through May 2, 1940.

Methods.—Direct smears of the peripheral blood were made according to my own method.[2] Both the smears and the bone marrow preparations obtained from patients with blood dyscrasias were stained with Wright's stain. Moist preparations of the whole blood were obtained by the method of Emmel.[4] They were kept at room temperature for forty-eight hours. Some preparations were kept for several months, but it was found that forty-eight hours is ample time for study of the erythrocytic structure. Within this length of time such untoward complications as hemolysis, multiplication of bacteria, growth of fungi (since the procedure is not sterile), reversion of the elements to their original shape and autoagglutination, although they do occur, usually are not so extensive as to interfere materially with the carrying out of the test. The moist preparations were observed immediately after the blood had been obtained and at the end of two, six, twenty-four and forty-eight hour intervals. In this way the untoward reactions were noted in time. In Negroes local anoxemia was produced before the blood was obtained

for the test. Both a direct smear and a moist preparation were obtained in each case, a complete blood picture studied and a brief history noted.

Patients.—The patients were from 3 weeks to 88 years old. There were 910 white persons (451 male and 459 female) and 692 Negroes (173 male and 519 female). Of the 692 Negroes, 45 (8 male and 37 female) showed a sickling trait. Sickle cell anemia was found in 7 patients (5 male and 2 female) and sicklemia (immediate and delayed) was found in 38 patients (3 male and 35 female). The incidence of the sickling trait in the Negro race was 6.5 per cent. There was not a single case of the sickling trait in the 910 white persons studied.

The patients with active sickle cell anemia were distributed according to age as follows: first decade 1, second decade 4, third decade 1 and fourth decade 1. It is rather a remarkable observation in this series that of the 37 females showing the sickling trait only 2 (5.4 per cent) had an active sickle cell anemia, whereas of the 7 males with the sickling trait 5 (71.4 per cent) suffered from an active sickle cell anemia.

Sicklemia was associated with syphilis in 7 patients (6 female; 1 male). It was associated with pertussis in 1, pregnancy in 1, recurrent carcinoma of the breast in 1, chronic salpingitis in 1, "chronic" appendicitis in 1, excessive menstruation in 1, acute pyelitis (also Trichuris trichiura and Enterobius vermicularis infection) in 1, acute gastritis in 1, retroflexion of the uterus with cystic ovaries in 1, hypertensive heart disease in 2 and uterine fibroids (leiomyomas) in 2. In none of these conditions accompanied by the sickling trait (sicklemia) did activation (sickle cell anemia) develop, nor was activation of the sickling trait observed in the 14 year old white boy (Ernest M., Johnny's brother, mentioned previously) who had had poliomyelitis in childhood.

In the course of this investigation it was found that while studying the sickling trait one should consider other blood dyscrasias in which erythrocytic structure plays an important role. The details of this study of closely related blood dyscrasias will be presented shortly in a separate paper.

COMMENT

According to Killingsworth and Wallace,[7] who surveyed the literature on this subject, the average incidence of the sickling trait in Negroes in the United States is 7 per cent. It is possible that in different localities and different countries some variations in the incidence of the sickling trait might be found, but for the study of the comparative incidence of this trait standardization of the criteria for the diagnosis and of the technic is desirable. For example, the time of observation of the moist preparations should be not less than forty-eight hours, as

7. Killingsworth, W. P., and Wallace, S. A.: Sicklemia in the Southwest, South. M. J. **29**:941, 1936.

has been pointed out. As far as the white race is concerned, in 8 cases of active sickle cell anemia (including 2 cases reported here) and 12 cases of sicklemia (including 7 cases reported here), the diagnosis appears to be founded on sufficient data to be considered as proved (table 1). The problem of whether this condition is confined to the Negro race or may occur in members of white and yellow races without admixture of Negro blood is not yet satisfactorily solved. However, it

TABLE 1.—*Cases of Sickle Cell Anemia in the White Race**

Year Reported	Authors	Patient: Sex and Age	Patient: Nationality	Patient: Place of Birth	Patient: Jaundice—J Spleen—S Liver—L	Sicklemia in the Family
1929	Cooley, T. B., and Lee, P.: Am. J. Dis. Child. **38**: 103 (July) 1929	M 4	Greek	Detroit	J—present S—enlarged L—not recorded	Mother
1932	Rosenfeld, S., and Pincus, J. B.: Am. J. M. Sc. **184**: 674, 1932	M 9	Italian	Brooklyn	J—present S—enlarged L—enlarged	Mother, sister
1934	Cooke, J. V., and Mack, J. K.: J. Pediat. **5**: 601, 1934	M 1	American	St. Louis	J—absent S—enlarged L—enlarged	Father
1934	Cooke and Mack	F 3	American (sister of preceding patient)	St. Louis	J—absent S—not enlarged L—enlarged	Father
1937	Haden, R. L., and Evans, F. D.: Arch. Int. Med. **60**: 135 (July) 1937	F 21	Sicilian	Sicily	J—present S—enlarged (removed previously) L—not recorded	Brother
1937	Haden and Evans	F 15	Sicilian (sister of preceding patient)	United States	J—present S—enlarged L—enlarged	Brother
1941	Ogden	F 9	Spanish	New Orleans	J—present (severe) S—not enlarged L—enlarged	Mother, brother, sister
1941	Ogden	M 8	German	Passaic, N. J.	J—present (mild) S—not enlarged L—enlarged	Mother, brother J., brother E., sister

* Some of the cases, for example those in Clarke's report of 2 cases of sickle cell anemia in a Sicilian family (Nebraska M. J. **18**: 376, 1933), are not included, since, according to the author, the father and son in that family possessed the characteristic appearance of Negroes.

appears to me that I have a right to my strong conviction that the sickling trait is a conditon found in the Negro race only and that in all cases in which members of white families have such a trait (in the active or inactive form) an admixture of Negro blood in the immediate, or occasionally even in the remote, ancestry has taken place.

So far, in not a single case has descent been definitely traced far enough back to establish beyond question the white ancestry of the person affected. By referring to table 1 it can be concluded that all white persons with sickle cell anemia reported on up to the present time have been persons of Mediterranean origin (Greeks, Italians,

Sicilians and Spaniards), with the exception of one American family, whose ancestry, however, was not traced sufficiently far back, and one German family (Johnny's), in which I was able to prove Negro ancestry.

Every living person, if one goes back twenty-four generations, allowing thirty years to a generation, had in the early thirteenth century 16,713,216 ancestors in the direct line.[8] If one considers this fact, it becomes obvious that it is practically impossible to exclude with any degree of certainty the existence of an admixture of Negro blood in some members of the white race (table 2).

Hannibal's invasion of Spain and Italy (218 B. C.), the Moorish occupation of southern Spain (711 A. D. to 1492 A. D.), slave trade

TABLE 2.—*Everybody's Ancestry*

	One Living Person Has	
First generation (present day)	2	parents
Second generation	4	grandparents
Third generation	8	great-grandparents
Fourth generation	16	great-great-grandparents
Fifth generation	32	
Sixth generation	64	
Seventh generation	128	
Eighth generation	256	
Ninth generation	512	
Tenth generation	1,024	
Eleventh generation	2,048	
Twelfth generation	4,096	
Thirteenth generation	8,192	
Fourteenth generation	16,384	
Fifteenth generation	32,768	
Sixteenth generation	65,536	
Seventeenth generation	131,072	
Eighteenth generation	262,144	
Nineteenth generation	524,288	
Twentieth generation	1,044,576	
Twenty-first generation	2,089,152	
Twenty-second generation	4,178,304	
Twenty-third generation	8,356,608	
Twenty-fourth generation	16,713,216	

with Africa, participation of Negroes in European wars and other historic circumstances brought the Negro race into close contact with the white. In the first case reported here the parents of the patient came from Nicaragua, which, according to the latest census, has about 750,000 inhabitants. Forty thousand are Indians, 2,000 are foreigners of various nationalities and the remainder are Spaniards. Although there are no Negroes in Matagalpa, a small town from which the parents of Gladys came, among the 6,000 residents of Bluefields a number of Negroes are domiciled. The great-great-grandparents of Gladys in both the maternal and the paternal lines came from Spain. Basing my conclusions on the study of a number of cases of sickling trait, including the 54 cases reported here, I assert, without any hesitation, that *presence*

8. Bloodless Phlebotomist, New York, The Denver Chemical Manufacturing Company, 1936, p. 21.

of the sickling trait in a white person is a definite proof of admixture of Negro blood in the immediate or remote ancestry. In no case of the sickling trait in a white person reported up to the present time has the possibility of admixture of Negro blood been definitely excluded. Since it also has been demonstrated that a simple dominant non-sex-linked mendelian character may be transmitted to the bearer's descendants for over four centuries,[9] and since the sickling trait follows the laws of such a transmission it is evident that if the admixture of Negro blood did not occur in the fourth or fifth generations of Gladys' family it might still have taken place as far back as four or five centuries, even at the time of the Moorish occupation of Spain. In this case the disease had been active since the patient's birth. During the first nine years of her life she had never been completely free from the clinicopathologic complex. The disease was also progressing during the last year that this patient was under my observation.

I was unable to find elsewhere in the literature a single proved case of the sickling trait in a person of Spanish descent and therefore believe that the case of sickle cell anemia and the 3 cases of sicklemia in persons of Spanish ancestry here presented are the first to be reported.

A case of the sickling trait in a white person to be acceptable should satisfy at least the following requirements:

1. Photographs of the affected person or persons, including members of the immediate family, in all cases in which this is possible, should be presented.

2. The family tree should be studied in detail for the purpose of confirming or rejecting the possibility of the existence of the sickling trait in every member.

3. A photomicrograph of the direct smear (in the active form) or of the moist preparation at the end of forty-eight hours (or before) should be presented.

4. The nationality and ancestry of the persons affected should be studied in reference to their residence. The history of the race to which the affected person belongs should be considered.

5. Admixture of Negro blood, if any, should be investigated, and any possibility of Mediterranean ancestry should be considered.

As far as the incidence of sickle cell anemia in any race is concerned, it should be admitted that the routine diagnostic procedures are

9. Boyd (A Text Book of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1938, p. 387) cites as an example a case of brachydactyly "transmitted from one of Henry the Sixth's nobles in the fifteenth century to descendants living at the present day; the recently exhumed skeleton of the original earl showed the same bony change."

inadequate. Many cases are missed because sickle cell anemia can be diagnosed by examination of the direct smear only in the clinically active periods. At times when the patient is in the stage of improvement, only a few sickle cells may be found, chiefly by my method of combined thick and thin smears and especially in the thin half of the slide. In the thick smear a few sickle cells, if present, are usually obscured by various non-sickled erythrocytes. As a rule, sicklemia is missed if only direct smears are made.

The sickling trait, as has been previously pointed out, can be diagnosed mainly by means of the moist preparation, and then only if it is kept not less than forty-eight hours at room temperature. I use the moist preparation as a part of the routine procedure for determining the blood count and am convinced that such a procedure should be generally accepted. As soon as a greater number of such tests are performed on blood from members of different races, more progress will be attained in determining the racial incidence of this condition.

SICKLE CELL ANEMIA AS A NATIONAL HEALTH PROBLEM

With the exception of the African continent, the largest number of the Negro population is domiciled in the United States, where, according to the 1940 census, there were 12,865,518 Negroes. The number of those having the sickling trait is 900,586, or 7 per cent of the total number.[7] These figures, of course, are approximate, but as close to the actual number as it is possible to estimate at the present time. The proportion of patients with active sickle cell anemia to the total number of sicklemic persons apparently has never been properly estimated, since in a number of cases active sickle cell anemia was evidently overlooked or diagnosed as some other disease, such as malaria, jaundice of unknown cause or rheumatic fever. Many children died in the first few months or even days of life from what appeared to be a deep "jaundice of undetermined origin."

In addition, there is marked confusion in the literature as to the proper meaning and definition of the term "sickle cell anemia." I cannot agree with those who state that sicklemia with anemia equals sickle cell anemia, as might be concluded from previously made definitions. Much credit goes to Sydenstricker,[6] Emmel,[4] Diggs and Bibb[10] and a number of other observers who clarified to a considerable extent many aspects of this question.

In spite of this the question still remains highly controversial. Dale[11] stated: "Among those individuals whose blood shows a sickle-

10. Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695 (Feb. 25) 1939.

11. Dale, G. C.: Sickle-Cell Anemia, South. J. Med. & Surg. **99**:14, 1937.

cell trait, or sicklemia, there will occur cases of sickle-cell anemia in a ratio estimated to be about 1 to 40 or 50." Sydenstricker [6] gave the ratio of sicklemia to sickle cell anemia as 9:1. Graham and McCarty [12] expressed the opinion that this ratio is rather high. However, in the present series the incidence of active sickle cell anemia among possessors of the sickling trait appears to be still higher, about 17 per cent.

Should the number of persons who manifest an active sickle cell anemia be taken as approximately 15 per cent (a proportion of 1 to 7), which, I believe, is quite close to the actual incidence, then, according to the figures given previously, an army of 135,088 people are doomed to complete extermination either in the first or in the second decade of life. Only a few survive until the third decade and still fewer until the fourth decade or later. It has also been proved that (as in both families here reported on) every sicklemic person is a potential bearer of sickle cell anemia and that, while not showing any marked clinical manifestations of the disease himself, he is capable of transferring it in active form to his progeny. Intermarriages between Negroes and white persons, which at one time were permitted in some states, may therefore directly endanger the white race by the transmission of the sicklemic trait.

MEDICOLEGAL SIGNIFICANCE OF THE SICKLEMIC TRAIT

I believe that the presence or absence of the sicklemic trait, because of its high incidence in the Negro race, may be of some service in certain medicolegal procedures, for example, the determination of paternity, as a supplement to the use of present knowledge in the realm of hemagglutinins.

SUMMARY

1. Nine examples of the sickling trait (2 of them of active sickle cell anemia) in 2 white families are hereby reported.

2. Familial incidence and hereditary transmission of the sickling trait in the maternal line are established in both these families. The mothers in both families had a delayed sicklemia, which possibly is an inactive, subclinical form of the disease, and each of them had transferred the disease in active form to at least 1 child and sicklemia to all the other children in her family.

3. The incidence of the sickling trait in 1,602 unselected patients of both the white and the Negro race was investigated. The sickling trait was found in 6.5 per cent of the Negroes. There was no instance of

12. Graham, G. S., and McCarty, S. H.: Sickle Cell (Meniscocytic) Anemia, South. M. J. **23**:598, 1930.

the sickling trait in 910 white persons studied in this series (9 cases reported in this article are not included).

4. The sickling trait is a condition found in the Negro race only, and the finding of such a trait in a member of another race indicates an admixture of Negro blood in the immediate or remote ancestry.

5. Of the 9 persons with the sickling trait in white families reported on in this article, 4 are apparently the only persons of Spanish nationality and 5 the only persons of German nationality ever reported in world literature as having this condition.

6. The use of moist preparations of the whole blood as a routine procedure in all cases and for patients of all races at the time when routine blood counts are performed is recommended.

7. For the purpose of more detailed study of erythrocytic variations in making all routine blood counts my technic for preparing blood smears is recommended.

8. Criteria for the diagnosis of the sickling trait in white persons are suggested.

9. Sickle cell anemia is a national public health problem, especially in the United States. Intermarriages between Negroes and white persons directly endanger the white race by transmission of the sickling trait, as has been proved in 9 cases here presented. Such intermarriages, therefore, should be prohibited by federal law.

10. A consideration of the sickling trait in medicolegal work is hereby proposed.

11. Of the 45 Negroes with the sickling trait 5.4 per cent of the females and 71.4 per cent of the males had an active sickle cell anemia.

12. In the first family reported in this article the mother had transferred the sicklemic trait to all her 3 children (to 1 in active form). In the second family the mother had transferred the sicklemic trait to all her 4 children (to 1 in active form). At the same time, the 3 sons inherited their father's blood group (A). Grouping of the blood of baby sister Joyce was not available.

SURGICAL TREATMENT FOR CIRRHOSIS

PROGNOSIS SUBSEQUENT TO OMENTOPEXY

HORACE B. CATES, M.D.
LOS ANGELES

During the last few years, a fairly large group of patients in the Los Angeles County Hospital who were found to have cirrhosis of the liver has been studied, and some of the results of the study have been published.[1] A phase of the problem involved in the treatment of those patients who have ascites leads to a consideration of surgical procedures. Apparently there is considerable difference of opinion among both internists and surgeons concerning the value of omentopexy as a therapeutic measure for patients who have this condition. It was considered worth while, therefore, to analyze the records of patients found to have cirrhosis and treated medically, giving special attention to the duration of their illness and to their life expectancy, and to compare these findings with those obtained from a study of the records of a similar group of patients who had received surgical treatment for ascites. The records of 5 patients who had had omentopexy done were obtained from a private hospital; all others considered in this study were from the Los Angeles County Hospital. Some recent concepts concerning physiologic changes related to disease of the liver and ascites are considered in the comment.

A brief résumé of previous reports dealing with the results of surgical treatment of patients who had cirrhosis and ascites is in order. The original suggestion of a surgical operation for the treatment of this condition was made by Talma [2] in 1898, but the first successful operation was performed in 1895 by Rutherford Morison,[3] whose patient lived two years following the operation. In 1904 Monprofit [4] tabulated

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1. Cates, H. B.: Relation of Liver Function to Cirrhosis of the Liver and to Alcoholism, Arch. Int. Med. **67**:383-398 (Feb.) 1941.

2. Talma, S.: Chirurgische Öffnung neuer Seitenbahnen für das Blut der Vena porta, Berl. klin. Wchnschr. **35**:833, 1898.

3. Drummond, D., and Morison, R.: A Case of Ascites Due to Cirrhosis of Liver Cured by Operation, Brit. M. J. **2**:728, 1896.

4. Monprofit, A.: Traitement chirurgical de la cirrhose du foie, Presse méd. **2**:667-670, 1904; cited by White, S.: Surgical Treatment of Ascites Secondary to Vascular Cirrhosis of the Liver, Brit. M. J. **2**:1287-1296, 1906.

the reports of 224 patients who had had the operation done and found that 84, or 37.5 per cent, of them had died within one month after the operation. In 70 patients, 31 per cent of the group, ascites subsequently disappeared and hemorrhage did not occur. Results of the Talma-Morison operation on 47 patients were reported by W. J. Mayo [5] in 1924 as being good, but the report contains no follow-up studies of the condition of this group. He considered that relatively slight risk was involved in the operation itself, but that ascites, hemorrhage and frequently edema of the lower extremities of these patients made any surgical operation a very serious procedure. The results of surgical treatment of 26 patients were recorded by W. Hughson,[6] who stated early in his skeptical review that a microscopic examination of a biopsy specimen of the liver is the only method by which an absolute diagnosis of cirrhosis can be made during life. He found the record of but 1 patient for whom the diagnosis had been made in this way. He concluded that surgical treatment of patients who have portal cirrhosis and ascites is without value. He found no evidence which indicated that any particular age, sex, race, period of disease or time of appearance of the ascites offered any particular hope of influence on the results that might be obtained by surgical treatment. The average mortality rate attributed to the Talma-Morison operation by Noetzel [7] is from 20 to 30 per cent and the number of cures 30 per cent, but the last statement is not supported by adequate follow-up records. Grinnell [8] treated 23 patients by performing omentopexy and found that 13 of them, 59 per cent, were unimproved. Six patients, 30 per cent of the total, died postoperatively, and 2, 9 per cent, were said to be free of symptoms.

Results of an analysis of the hospital records of 117 consecutive patients whose condition had been diagnosed as cirrhosis of the liver constitutes the basis of the first portion of the present report. The diagnosis was confirmed in 50 of these patients by examination with the peritoneoscope. Ninety-five, or 81 per cent, died, and of these 75 came to autopsy. Twenty-two were alive when this study was made. Eighty-six were males and 31 were females, and their ages ranged from the first to the eighth decade. According to serologic tests 33 had

5. Mayo, W. J.: The Surgical Treatment of Hepatic Cirrhoses, Ann. Surg. **80**:419-424 (Sept.) 1924.

6. Hughson, W.: Portal Cirrhosis with Ascites and Its Surgical Treatment, Arch. Surg. **15**:418-440 (Sept.) 1927.

7. Noetzel, W.: Zur Talma-Operation der Leberzirrhose, Arch. f. klin. Chir. **112**:153-156, 1919.

8. Grinnell, S.: Omentopexy in Portal Cirrhosis of the Liver with Ascites, Ann. Surg. **101**:891-901 (March) 1935.

syphilis, and gastrointestinal hemorrhage occurred in 37, in some instances as a terminal event. Sixty were jaundiced, and in 24 of these the icteric index was more than 60; in 9 it was more than 100. Ascites was present in 71, or 60 per cent of the group. Serum albumin and globulin were determined in 75 patients. The duration of life from the advent of symptoms regarded as diagnostically important, such as ascites, hemorrhage and jaundice, was noted. Other less relevant disturbances, such as diarrhea, loss of weight, peripheral neuritis and delirium tremens, symptoms complained of repeatedly, were disregarded, as they are not necessarily indicative of hepatic disease. The rate at which patients died after the onset of first symptoms definitely related to cirrhosis was as follows: within one month, 26; within two months, 42,

TABLE 1.—*Duration of Illness of One Hundred and Seventeen Patients* with Cirrhosis Treated Without Omentopexy*

1 month	26
1-2 months	16
2-3 months	9
3-6 months	14
6-9 months	12
9 months-1 year	7
1-2 years	15
2-3 years	8
3-4 years	4
4-5 years	2
5-6 years	2
10 years and over	2

* The intervals represent the time from onset of symptoms of cirrhosis until the patient's death, or to the time of his last interview at the Los Angeles General Hospital.

and within three months, 51, or 44 per cent of the group (table 1). During the first year, 84 died, during the second year 15 and during the third year 8. One hundred and seven, or 91 per cent of the group, died within three years of the onset of symptoms. Two patients lived for ten years after the onset. It is self evident that the type of patient with cirrhosis admitted to this institution has a poor prognosis. However, 40 per cent of this group were free of ascites and in order to make a comparison with a group of patients on whom omentopexy was performed, only those having ascites should be selected. The selection was arbitrarily made as follows: the records of consecutive patients who lived longer than one month following onset of symptoms and who had ascites at one time were analyzed as to duration of life or up to the time when they were last interviewed. This group comprised 53 patients. At the second month 14 patients, or 26 per cent, had dropped out, and at the end of one year 33, or 62 per cent, either were dead or

no longer returned to the hospital for examination. At the end of the second year, 6 patients had died and 3 were reported as still living—a total of 9. From two to ten years 6 patients had died and 5 remained alive (table 2). The following conclusions should be emphasized: First the patient in whom ascites develops has, on the whole, a better prognosis than those who have hemorrhage or a deep jaundice without ascites; second, it is obvious that the longer the patient has ascites the more favorable is the prognosis, if energetic medical therapy can be initiated.

It might prove profitable to review the impressions of other clinicians regarding the prognosis of cirrhosis. For instance, in 1892 White [9] stated that in his experience he had never seen a cirrhotic patient with ascites who survived long enough for a second paracentesis to be per-

TABLE 2.—*Duration of Life of Patients Having Ascites and No Omentopexy Who Lived Over One Month*

	Died	Living
1- 2 months	5	1
2- 3 months	6	2
3- 6 months	7	3
7- 9 months	5	1
10-12 months	3	..
1-2 years	6	3
2-4 years	4	3
5 years	1	1
10 years	1	1

formed. The average duration of life was only two months. However, his contemporary, W. B. Cheadle,[10] saw 23 patients who had cirrhosis and ascites, of whom 4 recovered and 2 were in fair health one year after they were first observed. The difference in results reported by these two observers might be explained by the fact that those of the second group who improved were induced to abstain entirely from alcohol. It was Cheadle's opinion that prompt relief of ascites by paracentesis prolonged the lives of his patients.

Later the mercurial diuretics were used in the treatment of this condition. Rowntree, Keith and Barrier [11] obtained encouraging results by the use of acetarsone, ammonium salts and a high carbohydrate diet.

9. White, W. H.: The Cause and Prognosis of Ascites, Guy's Hosp. Rep. **49**:1-42, 1892.

10. Cheadle, W. B., in Discussion in the Prognosis and Treatment of Ascites, Brit. M. J. **2**:1102-1106, 1892.

11. Rowntree, L. G.; Keith, N. M., and Barrier, C. W.: Novasurol in the Treatment of Ascites in Hepatic Disease, J. A. M. A. **85**:1187-1193 (Oct. 17) 1925.

After using this plan of management on a group of 112 patients, Snell [12] reported that the average duration of life after treatment was started was about sixteen months.

The prognosis of these patients is improved by the use of a diet high in carbohydrate, supplying adequate protein and supplemented by vitamins. After using such a regimen, Patek [13] reported the cases of 4 patients whose general condition improved and whose ascites disappeared. Since the publication of a report by Rich and Hamilton [14] I have been treating cirrhotic patients by giving large amounts of brewers' yeast and liver extract parenterally, with promising results.

The histories of 2 patients who survived ten years after the onset of cirrhosis are incorporated.

REPORT OF CASES

CASE 1.—*History.*—E. P., a 65 year old white carpenter, was admitted to the hospital Oct. 28, 1938. His first symptoms were noticed in 1928. At that time, after he had taken 49 pills for the treatment of arthritis painless jaundice developed and lasted five or six weeks. He had no chills or fever but noted clay-colored stools. His abdomen became extensively enlarged and remained so. During the last two years, he had also been troubled by an inguinal hernia (on the right side) and an umbilical hernia and was admitted to the Los Angeles County Hospital for herniorrhaphy. The past history revealed that he was treated for primary syphilis with mercury in 1900. He had drunk from 10 to 20 glasses of beer a day for twenty years, and had had an occasional glass of whisky, until 1935, three years before his admission to the hospital.

Examination.—Nothing unusual was seen about the head or neck. The heart's apex, while in the fifth interspace, was displaced to the anterior axillary line by subdiaphragmatic fluid. A harsh systolic murmur was present over the fourth left intercostal space and was transmitted to the axilla. The diastolic blood pressure was 135, the systolic pressure, 85. The lungs were essentially normal. The abdomen was greatly distended, and the abdominal veins were dilated. A "caput medusae" was noted. A small umbilical hernia was present. Shifting dulness and a fluid wave were demonstrable. A large, painful inguinal hernia was present on the right side. There was no edema of the extremities.

Laboratory Tests.—The blood count revealed 4,600 red cells per cubic millimeter, with a hemoglobin concentration of 85 per cent (13.6 Gm.). The white cells count was 3,800, with a normal differential.

There was definite melituria, but no acetonuria. The fasting blood sugar was 121 mg. per hundred cubic centimeters. On Oct. 31, 1938, his dextrose tolerance, after the ingestion of 2 Gm. of dextrose per kilogram of body weight, was as

12. Snell, A. M.: Clinical Aspects of Portal Cirrhosis, Ann. Int. Med. **5**:338-357 (April) 1931.

13. Patek, A. J.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329-330 (Nov.) 1937.

14. Rich, A. R., and Hamilton, J. D.: Experimental Production of Cirrhosis of the Liver by Means of Deficient Diet, Bull. Johns Hospkins Hosp. **66**:185-198 (March) 1940.

follows: first hour, 175 mg. per hundred cubic centimeters of blood; second hour, 220 mg.; third hour, 263 mg.; fourth hour, 308 mg.

The result of an echinococcus cutaneous test made on Nov. 1, 1938 was reported negative.

On Nov. 8, 1938 a peritoneoscopic examination was carried out, and 4,000 cc. of ascitic fluid was removed. Dr. John C. Ruddock reported as follows: "The peritoneal surface was clear. The liver was small, shrunken and nodular. The spleen was not recognized. There was a large right inguinal hernia. Conclusion: Atrophic cirrhosis."

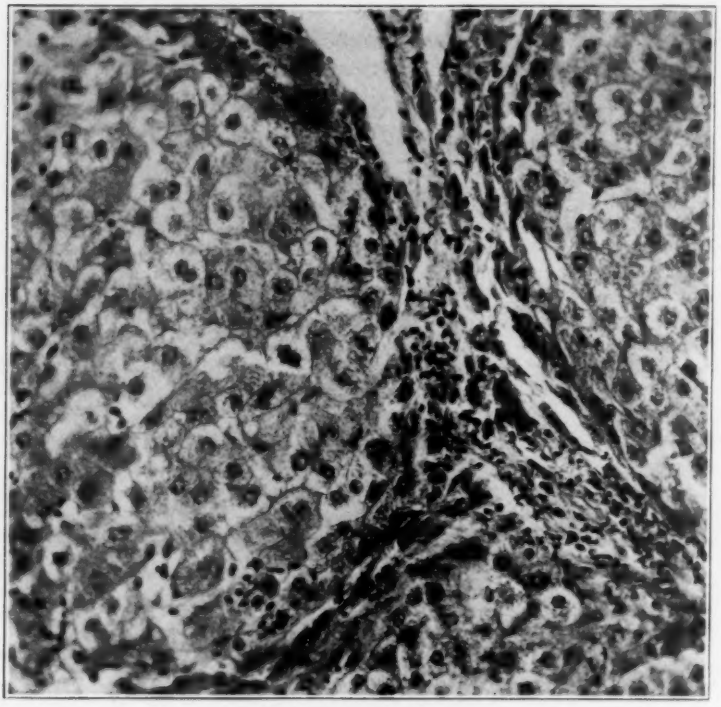

Fig. 1 (case 1 [E. P.]).—Slide showing the increased periportal tissue and disturbance of cellular structure of the lobules.

The report on the biopsy of tissue from the liver was reported as follows: "The specimen consists of a small portion of liver tissue, measuring 4 by 4 by 3 mm. Microscopic examination (paraffin serial sections) reveals that the lobular arrangement is considerably disturbed. There is moderate increase in the periportal connective tissue. The liver cells are well preserved for the most part. Hyperplasia of liver cells is evident in several areas. One or two small groups of necrotic liver cells are seen bordering the periportal connective tissue. There is moderate round cell infiltration of the latter with no polymorphonuclear leukocytes.

Alcoholic hyalin cannot be definitely identified. There is no fat in the liver cells (fig. 1). The diagnosis is hyperplastic nodule in Laennec's cirrhosis."

On Nov. 6, 1938 the patient's daily intake of protamine zinc insulin was raised from 10 units to 20 units, and a diet containing 128 Gm. of carbohydrate, 63 Gm. of protein and 80 Gm. of fat was prescribed. With this regimen his urine became free of sugar. Paracentesis was repeated on Nov. 27, 1938. Five liters of fluid was removed. The patient steadily improved and was discharged from the hospital on Dec. 9, 1938, with directions to have a truss made to support his inguinal hernia.

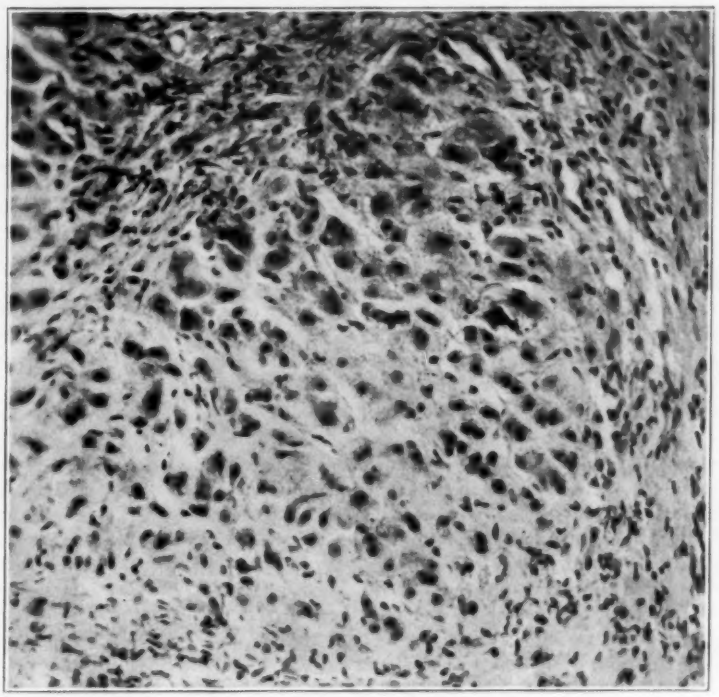

Fig. 2 (case 2 [A. B.]).—Slide showing the dilated, bile-stained ducts, marked periportal fibrosis and disturbed cellular structure of the lobules.

The patient's initial injury was a severe hepatitis, probably due to cinchophen given for the treatment of arthritis. He had discontinued drinking three years before his admission to this hospital. The diagnosis of diabetes and the use of insulin therapy not only made the urine sugar free but were conducive to hepatic regeneration, ultimately freeing the patient of ascites.

CASE 2.—*History.*—A. B., aged 34, was admitted to the hospital Nov. 7, 1938. He was born in Mesopotamia and came to the United States at the age of 22, in 1926. He stated that in 1928 he noticed a fulness and a dragging sensation in

the abdomen and felt a mass in the upper portion of the abdomen. One year after the onset he became increasingly yellow and turned very dark after exposure to sunshine. The abdominal distention was so distressing that splenectomy was performed in May 1930. His relief was of brief duration, and he was told that his liver was also enlarged. In 1931 he intentionally lost 20 pounds (9 Kg.) by using a special diet, and later he could not recover his former weight. He complained of nocturia, with urination three or four times a night, for five years until four months before his admission to the hospital. His gums had bled at intervals during the last year. The past history was uneventful except for measles and dysentery for one week while a child. He had frequent sore throats. He said he had not had any venereal disease and had never used alcoholic beverages.

Physical Examination.—Examination revealed a moderately emaciated man with deeply pigmented skin. The temperature was 99.2 F. The pulse rate was 88 and the respiratory rate 20 per minute. There was intense icterus of the scleras. The teeth were poor, and there was retraction of the gums. A few pinpoint hemorrhagic areas were seen. There was slight bulging of the lower part of the right costal margin. Excursion of the chest was poor, and crepitant rales were heard over the base of the right lung. The systolic blood pressure was 104 and the diastolic blood pressure 78. The apical impulse of the heart was visible in the fifth interspace at the midclavicular line, and a thrill was palpated at this point. The mitral first sounds were roughened. There were no cardiac murmurs. The abdomen was moderately distended. There was a midepigastric surgical scar, and amber fluid oozed from a paracentesis wound in the hypogastrium. Dulness was present in both flanks below the level of the umbilicus. The liver was palpable 4 cm. below the right costal sternal edge, firm and smooth and not tender to pressure. There was moderate scrotal edema.

Laboratory Tests.—The hemoglobin concentration was 68 per cent. The white blood cell count was 13,500, with normal distribution. The urine gave a 3 plus reaction for urobilinogen and the stool a 1 plus reaction. The fasting sugar content of the blood was 61 mg. per hundred cubic centimeters, the nonprotein nitrogen content 61 mg. and the cholesterol content 143 mg. The serum albumin content was 1.4 per cent cent and the serum globulin content 3.8 per cent. The icterus index was 100 units. The quantitative van den Bergh test indicated 11 mg. of bilirubin per hundred cubic centimeters of blood. The Wassermann reaction of the blood was negative.

Peritoneoscopic examination was done on November 10. Soluble pentobarbital U. S. P. (pentobarbital sodium) and morphine were administered preoperatively. Fifty-five hundred cubic centimeters of bile-stained fluid was removed. Dr. John C. Ruddock reported as follows: "All peritoneal surfaces are clear. The liver is brownish, small, sharp edged and irregular in shape, with multiple black nodules. The edge is curled up, and the left lobe is adherent to the diaphragm with adhesions which are continuous beneath the midline abdominal scar. The gallbladder is distended." Dr. Ernest Hall reported on a biopsy of tissue from the liver as follows: "The specimen consists of tissue from the liver measuring 5 mm. in diameter. Microscopic examination shows a notable disturbance of the normal architecture with considerable fibrosis about the periportal spaces, this being especially apparent about the interlobular bile ducts. Dense bands of fibrous tissue separate the liver cells into nodules of varying size. Some of the nodules are hyperplastic. Many of the liver cells are bile stained. The fibrous tissue is

moderately infiltrated with round cells. Many of the small bile ducts are plugged with bile. There is no increase in fat. The diagnosis is chronic biliary cirrhosis" (fig. 2).

Despite strenuous efforts in treatment the patient remained in a state of shock after the peritoneoscopic examination and died about eighteen hours later.

This patient's condition was so critical as to force one to conclude that any form of surgical intervention was contraindicated. There was marked elevation of the icterus index and of the total nonprotein nitrogen content of the blood. The serum proteins were definitely reduced. The sedatives employed are synergistic and must be detoxified by the liver. The operation was prolonged, and we now question whether saline solution given intravenously is actually of benefit in combating shock in this type of disease.

The total number of patients with ascites (table 3) who were treated by surgical methods was 38. The majority of them were 40 to 60

TABLE 3.—*Pertinent Data Concerning Ascitic Patients Subjected to Omentopexy*

Total number of cases (30 males, 8 females)					38
Total number of patients with alcoholism					21
Total number of positive Wassermann reactions					13
Total number having jaundice					21
Total number of hemorrhages					2
Peritoneoscopic examinations					24
Decades of life	2nd	3rd	4th	5th	6th
	3	5	12	13	5
Number of patients recorded as living				10	
Number of patients recorded as dead				28	
Postoperative deaths, two weeks				16 (42 per cent)	

years old. Twenty-one of this group gave a definite history of alcoholism, but it is our belief that the number of patients with alcoholism was actually higher. Thirteen showed serologic evidence of syphilis. The incidence of hemorrhage among the group selected by the surgeons was remarkably low, there being only 2 cases, although 21 patients at some time were jaundiced to some degree. Peritoneoscopic examinations were made on 24, and on several biopsies of the liver were done at the same time. Twenty-eight of those patients are known to be dead. Sixteen, or 42 per cent of the group, died within two weeks after having been operated on. Of the remaining 12 patients, 10 had died within six months subsequent to the operation, making a total of 68 per cent of the entire series of patients. Of the 10 remaining patients, 6 are known to have been alive 6 months after operation. One lived 3 years and 11 months. For more complete details regarding these patients, particularly regarding the laboratory work which was done, together with the data compiled subsequent to surgical intervention refer to table 4.

TABLE 4.—*Data on Patients*

Patient	Sex	Age	Wassermann Reaction *	Alcoholism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm. per 100 Cc.		Hemorrhage
								Albumin	Globulin	
1	M	41	0	Alc.	6/28/35; 1 week, ascites	+	Jaundice; 7/2/35, 53 units, 5 mg.	...	...	0
2	M	52	0	Alc.	8/10/38; 1½ years, ascites	+	8/13/38, 38 units; 8/17/38, 36 units; 8/24/38, 20 units; 9/ 6/38, 31 units; 9/17/38, 27 units; 9/24/38, 33 units	8/13/38: 2	3.3	0
								8/17/38: 2	2.9	
								9/17/38: 1.9	3.8	
								9/24/38: 1.75	2.5	
3	F	25	+	Alc. (1-2 glasses of beer daily)	9/10/39; 1 month, ascites	+	9/12/39, 20 units	.....		0
4	M	26	0	Alc., not heavy	6/15/35; 4 weeks	+	6/20/35, 19 units, 1.2 mg.	.....		?
5	M	53	0	Alc.	5/7/34; 3 weeks	0	5/7/34, 100 units, 17.5 mg.	.....		0
6	M	57	0	Alc.	7/24/37; 8 months	+	7/25/37, 20 units	7/25/37: 2.3	2.9	..
7	M	55	+++	....	7/1/38; 7 months	6 liters	6/29/38, 60 units, 4 mg.; 7/ 4/38, 52 units; 7/ 7/38, 62 units; 7/18/38, 73 units	.....		..
8	M	56	0	....	3/18/30; 3 weeks	+	3/29/30, 6 units	.....		+
9	M	32	0	No alc.	2/11/38; 1 month before ascites	+	2/21/38, 10 units; 3/ 7/38, 7 units	2/15/38: 2.8	2.7	0
								3/7/38: 3.06	2.6	
10	M	45	0	Alc. ?	8/28/37; 4 weeks; 10/26/37, admission	++++	11/2/37, 10 units	.....		Epistaxis
11	M	46	0	Alc.	10/26/40; 3 years, ascites	3 years	.....	.....		..

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
7/22/35, microscopic examination, extensive cirrhosis, portal type, with fatty changes	7/22/35; liver hard, sclerotic, not typically hobnailed; omentum sutured to posterior sheath of right rectus	1 day	7/6/35; liver nodular; possible syphilitic cirrhosis	.....	7/22/35 Died; no autopsy
8/17/38, galactose tolerance, 1.4 Gm.	10/7/38; omentum split, placed on both sides of incision beneath rectus muscles	2 days	.....	.....	10/9/38 Died; no autopsy
9/14/39; biopsy: lymphocytes, ++; polymorphonuclears ++; fat, ++; necrosis, ++; subacute alcoholism, cirrhosis	10/9/39; omentopexy, cholecystectomy; no gallstones; omentum spread under surface of recti	2 days	9/14/39; early cirrhosis	.....	10/11/39 Died; no autopsy
6/17/35, hemoglobin 72%; red blood cells, 2,900,000; white blood cells, 28,000	7/8/35; cirrhosis of liver; microscopic section; omentum placed under right rectus muscle; spleen 3 times normal size; duration 1 hr. 10 min.; ¼ grain (0.015 Gm.) morphine sulfate, 1 cc. dial and ethylene	3 days (cholecystectomy; gastric dilatation; acute ileus, secondary)	6/29/35; liver essentially normal; microscopically, multiple hepatic adenoma	.....	7/11/35 Died; no autopsy
5/31/34; microscopic examination, extensive necrotic and fatty changes, inflamed and fibrous proliferation	5/31/34; preoperative diagnosis, possible carcinoma of head of pancreas or cirrhosis; pancreas normal; omentopexy, omentum spread between fascia and subcutaneous fat	3 days	.....	Malaria 20 years previously	6/3/34 Died; no autopsy
.....	8/21/37; liver moderately enlarged, spleen 4 times normal size; omentum between peritoneum and muscle	4 days	8/7/37; advanced cirrhosis; liver very small, rough, nodular	.....	8/25/37 Died; no autopsy
.....	7/21/38 (H. G. S.); preoperative diagnosis, obstructive jaundice or biliary cirrhosis; postoperative diagnosis, cirrhosis of liver, splenectomy and omentopexy; pantopon,† nitrous oxide and ethylene anesthesia; duration, 1 hr. 15 min.	4 days	.....	.....	7/25/38 Died
.....	5/8/30; omentopexy; liver nodular, hard and small; ether, 150 Gm.; operation lasted 1 hr. 10 min.	5 days (H. G. S.)	.....	.....	5/13/30 Died
2/12/38; Takata-Ara reaction negative; 2/15/38, Takata-Ara reaction +	4/19/38; liver about ½ normal size; spleen 3 times normal size; omentum placed under rectus muscle	5 days	4/10/38; liver small, shrunken; atrophic cirrhosis	.....	4/24/38 Died; liver 1,400 Gm.; spleen 850 Gm.; cirrhosis severe; anatomic evidence of collateral circulation
.....	1/15/38; small hobnailed liver; anterior surface of liver traumatized; omentum placed between posterior and anterior sheath of rectus muscle	6 days	11/4/37; atrophic cirrhosis	.....	1/21/38 Died
.....	11/29/40 (H. G. S.); omentopexy; liver aspirated; liver small, nodular; spinal anesthesia; operation lasted 1 hr. 20 min.	1 week	.....	.....	11/26/40 Died

TABLE 4.—*Data on Patients*

Patient	Sex	Age	Wassermann Reaction *	Alcoholism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm. per 100 Cc.		Hemorrhage
								Albumin	Globulin	
12	M	41	+	Alc. (1 gal. wine per week and whisky)	2/27/40; 2 weeks	+	4/3/40, 95 units	2/27/40, total protein 6.7 Gm.		..
13	M	44	0	Alc. ?	2 months; ascites before admission, 5/15/35	+	No jaundice	.....		0
14	M	54	+	....	2/3/37; 6 weeks	..	2/17/37, 9 units	2/17/37 2.28	2.9	..
15	M	47	0	Alc.	12/30/34; incidental illness	..	.....	.....		..
16	M	48	+	Alc.	8/19/38; 4 weeks	..	8/21/38, 36 units	.....		—
17	M	30	0	Alc. (1 gal. beer per week)	10/14/39; 1 month	+	10/14/39, 40 units; jaundice; 3/25/39, 11 units	.....		—
18	M	55	+	Alc.	9/10/38; 1 month	+	9/28/38, 12 units	11/18/38 2.9	3.3	0
19	M	67	?	....	7/14/34; 6 months, ascites; 2/6/37, entered hospital	+ 12/17/34, 20 taps, Preoperative, patient home until 2/6/37; 3/26/37, ascites recurred and patient in coma	3/25/37, 9 units	3/25/37 2.15	2.2	0
20	F	49	0	Alc., light	4/9/36; 6 months (before ascites)	+	4/9/36, 7.1 units	.....		0

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
2/21/40, biopsy, necrosis ++, evidence of alcoholism, hyalin and chronic cirrhosis; 3/4/40, cholesterol, 176 mg., 38% esters; 3/21/40, prothrombin 20%	3/27/40; operation time 69 min.; omentopexy; cyclopropane; omentum laid triangularly beneath rectus fascia	1 week	3/20/40; nodular, pale, irregular liver; advanced cirrhosis	.....	4/4/40 Died; liver 1,890 Gm.; spleen 530 Gm.; 3,000 cc. fluid; generalized peritonitis; Laennec's cirrhosis
Hemoglobin, 75%; red blood cells, 3,000,000	6/3/35; transverse incision; omentum in split muscles and over peritoneum; spleen not removed	9 days	5/18/35; Banti's disease, strongest possibility	.....	6/12/35 Died; liver 950 Gm.; spleen 1,050 Gm.; splenic vein incompletely filled with old antemortem thrombus; diagnosis: portal phlebosclerosis and chronic congestive splenomegaly and early hepatic cirrhosis; portal thrombosis and hepatic necrosis
.....	3/26/37; omentopexy	2 weeks	3/20/37, small shrunken, fibrous, granular liver; atrophic cirrhosis	.....	4/7/37 Died; no autopsy
.....	1/7/35 (H. G. S.); omentopexy; preoperative diagnosis, chronic cholecystitis; liver twice normal size; acute hepatitis, minimal ascites; operation lasted 29 min.	2 weeks	.....	.....	1/21/35 Died; no autopsy
.....	9/10/38; liver smaller than normal; liver traumatized; omentum attached to peritoneum; ether and cyclopropane; operation lasted 1½ hr.	2 weeks	8/25/38; small, rough, hobnailed liver; atrophic cirrhosis	.....	9/26/38 Died; no autopsy
10/29/38, cholesterol, 63 mg., 39% esters; prothrombin 32%; 11/20/39, prothrombin normal; 1/25/39, cholesterol, 172 mg., 37% esters	2/2/39; hobnailed, markedly shrunken liver; dome of liver scarified; omentum sutured in muscle and fascia	4 months	11/2/39; cirrhosis; liver normal size, but small nodules; 12/21/39; characteristics of advanced cirrhosis	Typhoid; 11/3/39; biopsy lymphocytes +; necrotic cells +; slight fat; evidence of alcoholism; hyalin ++; chronic cirrhosis	4/3/40 Died; liver 1,500 Gm.; spleen 350 Gm.; portal cirrhosis with hemorrhage from esophageal vein
.....	2/24/39; marked cirrhosis; omentum attached posterior to rectus muscle	7 months	10/1/38; ascitic, nodular, rough and granular liver; atrophic cirrhosis with numerous areas of regeneration	.....	10/9/39 Died; no autopsy
.....	8/10/34; liver somewhat shrunken; left rectus incision; peritoneum sutured beneath muscle and subcutaneous tissue	3 years, 8 months	8/6/34; atrophic hobnailed liver	.....	4/14/37 Died; liver 800 Gm.; spleen 600 Gm.; atrophic cirrhosis and arteriosclerotic heart disease
.....	4/29/36; liver shrunken to ⅔ normal size, nodular, hard; some adhesions at dome of diaphragm; surfaces of liver roughened; omentum sutured to anterior abdominal peritoneum	7 weeks	4/18/36; atrophic cirrhosis; granular, irregular wrinkled liver	.....	6/20/36 Died; no autopsy

TABLE 4.—*Data on Patien*

Patient	Sex	Age	Wassermann Reaction *	Alcoholism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm. per 100 Cc. Albumin	Protein, Gm. per 100 Cc. Globulin	Hemorrhage
21	M	47	0	Alc.	8/20/35; 2 weeks	+ recurring ascites	8/20/35, 26 units; 8/22/35, 20 units; 8/24/35, 10 units; 8/28/35, 9 units; 9/ 8/35, 75 units; 9/12/35, 87 units; 9/24/35, 8.8 units	8/20/35 3.4 8/28/35 2.8 8/31/35 2.9 9/8/35 3.5 9/14/35 2.8 9/24/35 2.8 8/26/36 3.3 3/10/37 2.9	1.8 1.6 2.1 2.1 2.1 1.8 2.3 2.1	..
22	M	68	0	Alc. ?	4/14/32; 12 months; ascites before	+	0	.....		0
23	M	54	+	Alc. (wine)	5/2/34; 6 days before	..	6 days, jaundice; 5/22/34, 80 units; 5 mg.; 5/2/34, 200 units	.....		0
24	F	48	..	....	8/7/38; ascites, 2 months	..	8/9/38, 11 units	8/10/38 2.5	3.0	..
25	M	54	++++	Alc.	5/3/38; 6 weeks before	+	5/4/38, 15.7 units	5/4/38, 1.16 Gm. total protein 5/4/38 2 6/19/38 2.2	2.6 3.8	..
26	M	39	+	Alc.	7/24/38; 6 months	..	7/26/38, 14.8 units	8/3/38, total protein 5.8 Gm.		
27	M	53	0	Alc.	2/12/38; 6 days	+	.....	.....		..
28	F	62	..	....	10/20/37; 6 years	+	12/22/37, 10 units; 9/15/30, 60 units; 1/11/39, 37 units	12/22/37 3.1 2/7/38 2.7 9/15/38 3.4	3.6 3.2 3.8	..
29	M	48	0	Alc. (whisky daily)	9/25/39; 5 months	+	10/2/39, bromsulphalein excretion 40%; hippuric acid test, 2.2 Gm.; 9/30/39, 5 units	9/29/39 1.8 9/26/39 2	2.4 2.3	..

n Patien Subjected to Omentopexy—Continued

Hemorrhage	Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
..	....	1/9/37; liver unusually large, not hobnailed, rather roughened; omentum sutured to anterior peritoneum posterior to muscle	5 months	.....	2/9/37, paracentesis; 2/16/37, 4,500 cc.; 3/8/37, 2,500 cc.	6/8/37 Died; no autopsy
0	.....	4/12/32; hobnailed liver; spleen enlarged; omentum sutured outside peritoneum	2 months	.....	.....	6/12/32 Died; no autopsy
0	.....	6/6/34; liver hobnailed, portal cirrhosis; omentum brought through peritoneum and laid laterally on it	6 months	.....	.....	12/17/34 Died; jaundice grade 3; hobnailed liver, grade 3; spleen, grade 3; chronic cirrhosis with ascites and jaundice; coroner's case
..	Bromsulphalein excretion, 27%; galactose tolerance test, no galactosuria	8/16/38 (H. G. S.); omentopexy; duration 30 min.; spinal anesthesia	10 weeks	.....	.....	10/3/38 Died; exploratory laparotomy; ascites 6 liters, no pathologic condition found
..	.....	5/26/38: omentopexy; omentum placed beneath rectus sheath in fan-shaped arrangement; nupercaine, local and spinal anesthesia	1 month 10 days	5/12/38; irregular, nodular, fibrotic liver; capsule thickened; Laennec's cirrhosis and ascites	Tropical dysentery	7/6/38 Died; heart 250 Gm.; no syphilitic heart disease; omentum, many small vessels traversing anastomosis; parietal peritoneum; liver 1,000 Gm.; spleen 250 Gm.; atrophic cirrhosis, anasarca, subacute peritonitis
	.....	10/6/38; Mayo omentopexy; omentum laid posterior to rectal fascia, in fan-shaped arrangement; ether, ethyl chloride anesthesia	Unimproved paracentesis repeated; 4 months	7/30/38; advanced cirrhosis; liver small, nodular	.....	2/11/39 Died; no autopsy
..	.....	3/14/38; liver, small, atrophic; omentum spread over right rectus sheath into subcutaneous fat; cyclopropane; operation lasted 44 min.	7/21/38, not improved; 3 months	2/29/38; atrophic cirrhosis; liver small, wrinkled	.....	7/25/38 Died; no autopsy
..	9/15/38, cholesterol, 177 mg., 60% esters	9/30/38; liver hobnailed; ascites; dome roughened; omentum sutured in rectus and subcutaneous tissue; operating time 1 hr.; local anesthesia, procaine hydrochloride	2 months	.....	.....	1/13/39 Died; coroner; chronic hepatic cirrhosis
..	9/29/39, microscopic biopsy, occasional necrotic cells, evidence of alcoholism, hyalin ±, chronic cirrhosis	10/6/39; omentum sutured to edges of peritoneum	12/22/39, no ascites for 7 weeks since operation; 12/22/39, last heard from	9/28/39; hobnailed liver; chronic cirrhosis and ascites	.....	.....

TABLE 4.—*Data on Patien*

Patient	Sex	Age	Wassermann Reaction *	Alcoholism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm. per 100 Cc. Albumin	Protein, Gm. per 100 Cc. Globulin	Hemorrhage
30	F	28	0	No alc.	1/29/40; 1 year	+	.....	.....		..
31	M	32	+	Alc.	7/2/35; 1 month	+	7/9/35, 5.5 units	7/9/35, total protein 7.2 Gm.		0
32	M	57	+	Alc. ?	8/19/36; 1½ months; jaundice before	+	+ 6/30/36, 20 units	3/12/37 2.5 2/17/37 2.2 1/28/37 2 12/10/36 1.9 12/5/36 2.1	3.8 3.3 3.5 3.3 2.9	0
33	F	61	+	....	2/2/34; 4 months before	+	2/2/34, 12 units	.....		..
34	M	53	0	Alc.	4/21/34; 3 months before	+	4/21/34, 20 units	.....		..
35	F	46	+	No alc.	4/4/34; 6 months ascites	+	4/4/34, 10.5 units	.....		..
36	M	55	0	Alc.	7/25/39; 1 month	+ repeated taps since onset	.....	10/27/39 2.1	1.9	..
37	F	64	+	Alc. ?	4/20/38; hematemesis, 1 day	+	.....	.....		12/5/38; hemorrhage repeated
38	F	35	0	Alc. for 15 years	12/5/37; 9 months; before operation	11/10/38	12/9/37, 26 units; 2/ 7/38, 5 units	12/21/37 2.2 12/23/37 2.5 2/7/38 2.1	2.9 2.7 2	..

* In this column, 0 indicates negative reaction.
† Pantopon is a mixture of hydrochlorides of opium alkaloids.

Subjected to Omentopexy—Continued

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
2/15/40, Takata-Ara reaction +	4/4/40; liver smooth, slightly enlarged; omentum attached to posterior surface of rectus muscles	12/27/40, still alive, apparently well	.....	11/22/40, ventral hernia	.....
.....	4/9/37; trauma of dome of liver; omentum sutured to subcutaneous tissue of abdomen	5/15/40, light work; 8/19/40, patient still alive and in jail	8/24/35; atrophic cirrhosis	Tuberculosis moderately advanced, bilateral, chronic, 10/18/35; from 10/7/36 to 3/26/37 patient had 43 injections of salyrgan; from 5/5/37 to 10/7/37 had 32 injections of mersalyl	.....
.....	10/10/36; omentum laid on anterior surface of parietal peritoneum	3/1/38, still alive, 17 months	8/22/36; atrophic cirrhosis	Malaria therapy, 5/7/36, for syphilis of central nervous system; 8/15/37, paracentesis of abdomen, 2,200 cc. in toto; thoracentesis, 1,900 cc.; 12/26/36, abdominal fluid disappeared; hydrothorax occurred after operation	.....
.....	4/14/34; hepar lobatum; left rectus incision; omentum placed beneath rectus muscle and remainder under subcutaneous tissue	No return after discharge, 4/30/34	2/17/34; malignant mass involving gallbladder and liver	.....	.....
5/10/34; microscopic section, mild grade of cirrhosis	5/10/34; omentum spread between muscle and fascia of abdomen	5/13/36, still alive with incisional hernia; still has ascites, 2 years	4/27/34; cirrhosis; atrophic liver	.....	.....
.....	7/5/34; liver small, hard, nodular and granular; omentum attached to anterior parietal peritoneum; spinal anesthesia; liver 6 times normal size; surface dome of liver traumatized	9/19/34, discharged to county farm	4/7/34; cirrhosis; liver atrophic	Paracentesis repeated after operation	.....
7/26/39; total protein, 7.4 Gm.; 12/12/39, total protein, 6.7 Gm.; 10/27/39, cholesterol, 135 mg., 33% esters	11/1/39; omentum extensively adherent beneath wound in upper part of abdomen, which caused considerable hemorrhage when abdomen was opened; large plaque of omentum placed under medial rectus flap; operation lasted 1 hr.; procaine hydrochloride spinal anesthesia	1/4/40, still alive, 2 months; no very definite effect from omentopexy; 1/12/40, discharged	.....	.....	.....
.....	5/20/38; preoperative diagnosis, bleeding gastric lesion; postoperative diagnosis, hemorrhage from esophageal varices; 500 cc. ascitic fluid; liver ¼ normal size; omentum sutured to inferior rectus sheath; ether	12/19/39, last heard of; 18 months	.....	.....	.....
12/21/37, Takata-Ara reaction +	9/26/38; omentopexy; preoperative diagnosis, cirrhosis and ascites	9/2/39, still alive, 1 year	4/21/38; perihepatitis; capsular cirrhosis	.....	.....

COMMENT

Although the postoperative mortality rate of this group of patients on whom omentopexy was performed is high, it is not correct to maintain that either the skill of the surgeon or the subsequent care of the patient was inferior to that of thirty years ago. Competent surgeons did these omentopexies. The problem involved raises the following questions: Can any form of surgical treatment greatly benefit these patients? Can the disturbance of physiologic function be corrected by mechanical intervention? Are the alterations in the general physiologic status of these patients responsible for the high operative mortality, and if so, how and to what degree can physiologic balance be restored by preoperative management?

The diminution of the serum proteins found in patients who have cirrhosis is responsible for important physiologic readjustments. Tumen and Bockus [15] concluded that hypoalbuminemia was the most constant alteration of the serum proteins. This condition was found at one time or another in all of their patients who had chronic, advanced disease of the liver. Myers and Keefer [16] found a deficiency of total serum protein in 16 patients, and the decrease in albumin was most pronounced. By repeating plasmapheresis on dogs until edema appeared, Weech, Goettsch and Reeves [17] found that their plasma albumin values were below normal. They noted that ascites was invariably present after repeated plasmapheresis, but that edema of the extremities was less intense than when the dogs were subjected to low protein nutritional experiments. Melnick and Cowgill [18] found that the dog, even when subjected to prolonged intensive plasmapheresis for sixteen weeks, shows no impairment of its ability to regenerate plasma proteins. This restorative facility, however, is injured in cirrhosis. Myers and Keefer [16] gave their 4 ascitic patients diets with a high protein content (100 to 300 Gm. daily) without success in increasing their levels of blood protein. Investigators [19] pointed out that there is a reduced blood volume coexistent with the depleted

15. Tumen, H., and Bockus, H. L.: The Clinical Significance of Serum Proteins in Hepatic Diseases, Am. J. M. Sc. **193**:788-800 (June) 1937.

16. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, Arch. Int. Med. **55**:349-359 (March) 1935.

17. Weech, A. A.; Goettsch, E., and Reeves, E. B.: Nutritional Edema in the Dog, J. Exper. Med. **61**:717-734 (May) 1935.

18. Melnick, D., and Cowgill, G. R.: The Influence of Prolonged Intensive Plasmapheresis upon the Ability of the Organism to Regenerate Serum Protein, J. Exper. Med. **66**:493-508 (Oct.) 1937.

19. (*a*) Chang, H. C.: Plasma Protein and Blood Volume, Proc. Soc. Exper. Biol. & Med. **29**:829-832 (April) 1932. (*b*) Melnick, D., and Cowgill, G. R.: The Serum Protein Complex as a Factor in Regulating Blood Volume, ibid. **35**: 312-314 (Nov.) 1936. (*c*) Lepore, J.: Relation of Plasma Volume to Plasma Protein Concentration, ibid. **30**:268-269 (Dec.) 1932.

protein reserves and depressed plasma protein. These fluctuations in volume are considerable. For instance, Lepore [19e] estimated a dog having plasma albumin of 3.82 Gm. per hundred cubic centimeters to have a blood volume of 1,414 cc. The plasma albumin was reduced to 2.14 Gm., and the existing blood volume was changed to 1,073 cc. He found a rather constant and direct relationship between the plasma albumin concentration and the plasma volume.

In their studies of secondary traumatic shock, Gasser, Erlanger and Meek [20] stated that diminished blood volume is the only constant factor tending toward failure of circulation. Roome, Keith and Phemister [21] found decreased blood volume when the blood pressure was lowered by hemorrhage, trauma to the extremities or manipulation of the intestines. Under these conditions, with the associated diminished circulating blood volume, the experimental animal is less likely to survive another hemorrhage or operation than to survive other circumstances in which the blood pressure is depressed by shock to a similar degree.

Blalock [22] stated that when rapid hemorrhage occurs there is a diminution in the circulating blood volume, but that because of vasoconstriction the blood pressure is unaltered. If the hemorrhage continues the blood pressure drops in spite of vasoconstriction. Later Minot and Blalock [23] defined shock as a condition due to peripheral vascular failure resulting from a discrepancy between the size of the vascular bed and the volume of circulating blood.

It is maintained that when the plasma proteins, more specifically the albuminous fraction, are reduced to a critical level, edema and a decrease in the circulating blood volume result, and these changes account in part for the high death rate following omentopexy.

Sordes and parched tongue are common both in malnutrition and in advanced cirrhosis. Evans and Shulman [24] caution against giving parenterally large amounts of saline fluids to malnourished patients. On account of their hypoproteinemia there is also a disturbance of capillary and extracellular osmotic equilibrium, so that anasarca develops and they have fatal pulmonary edema or eclamptic-like convulsions. However, in those instances in which cirrhosis and ascites are present, the recom-

20. Gasser, H. S.; Erlanger, J., and Meek, W. J.: Studies in Secondary Traumatic Shock, Am. J. Physiol. **50**:31-53 (Oct.) 1919.

21. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock, Surg., Gynec. & Obst. **56**:161-168 (Feb.) 1933.

22. Blalock, A.: Shock: Further Studies with Particular Reference to the Effects of Hemorrhage, Arch. Surg. **29**:837-857 (Nov.) 1934.

23. Minot, A. S., and Blalock, A.: Plasma Loss in Severe Dehydration, Shock and Other Conditions as Affected by Therapy, Ann. Surg. **112**:557-567 (Oct.) 1940.

24. Evans, J. A., and Shulman, H.: On Danger of Forcing Fluids in Malnutrition, Am. J. M. Sc. **199**:237-246 (Feb.) 1940.

mendations of Coller, Dick and Maddock [25] concerning the control of water exchange in postoperative patients by checking the urinary output are futile, since ascitic patients ordinarily have oliguria. The persistent drainage from the abdominal wound following omentopexy, while beneficial in some respects, further obscures the true status of the patient's water balance. The only measures of value are those which raise and maintain the serum proteins to a normal level. Actually the loss in ascitic fluid of serum and proteins which are utilized for the process of repair further lessens the already depleted reserves. Even with impending edema, Drew, Scudder and Papps,[26] who controlled hydration by means of the hematocrit and determinations of the specific gravity of the blood and of the plasma protein, had no method of adequately rehydrating the blood after surgical procedures.

Symptoms once attributed to portal obstruction, such as nausea, a flatulent type of dyspepsia, constipation and occasional bouts of diarrhea, can in part be interpreted as due to dysfunction of the gastrointestinal tract because of the depletion of proteins.

Jones, Eaton and White [27] found that experimental edema involved not only the subcutaneous tissues but all the organs. Proceeding further with the analysis of physiologic disturbances due to the lowering of the plasma proteins to critical levels, Barden, Ravdin and Frazier [28] showed by roentgen studies a marked delay in gastric emptying in both experimental animals and postoperative patients. The gastric emptying time varied inversely with the concentration of plasma protein. Barden and his co-workers [29] found a marked retardation of intestinal motility in dogs in which hypoproteinemia had been produced. Thompson, Ravdin and Frank [30] found that this delay was corrected after the restoration of plasma proteins to normal levels.

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25. Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, J. A. M. A. **107**:1522-1527 (Nov. 7) 1936.

26. Drew, C. R.; Scudder, J., and Papps, J.: Controlled Fluid with Hematocrit, Specific Gravity and Plasma Protein Determination, Surg., Gynec. & Obst. **70**:859-867 (May) 1940.

27. Jones, C. M.; Eaton, F. B., and White, J. C.: Experimental Postoperative Edema, Arch. Int. Med. **53**:649-674 (May) 1934.

28. Barden, R. P.; Ravdin, I. S., and Frazier, W. D.: Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of the Billroth I or II Types, Am. J. Roentgenol. **38**:196-202 (July) 1937.

29. Barden, R. P.; Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Influence of Serum Protein on the Motility of the Small Intestine, Surg., Gynec. & Obst. **66**:819-821 (May) 1938.

30. Thompson, W. D.; Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, Arch. Surg. **36**:500-508 (March) 1938. Thompson, W. D.; Ravdin, I. S.; Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, ibid. **36**: 509-518 (March) 1938.

The high mortality rate of the patients who were operated on can be ascribed to undernutrition. It was emphasized that they are more susceptible to shock, that edema of the gastrointestinal organs predisposes to tympanites because of decreased peristalsis and that, in addition, their surgical wounds will not heal normally.

There is, however, another aspect of the condition of patients having cirrhosis and ascites which contraindicates operation. Anesthesia induced by one drug or another naturally is used. Adriani [31] states that anesthetics are detoxified primarily by the liver, although the kidney and other tissues play lesser roles. Nevertheless, the surgeon is prone to neglect this important fact, feeling secure in the idea that the newer technics of anesthesia are so superior that there is now but a minimal risk.

Mousel and Lundy [32] concluded that, with the possible exception of barbital and phenobarbital, all other hypnotics should be administered with caution. A case is cited, in which afterward the condition was diagnosed as far advanced cirrhosis of the liver, in which pentothal sodium was administered to the patient before peritoneoscopic examination; instead of recovering from the action of the drug in ten minutes he continued to sleep for twenty-four hours. Cameron and de Saram,[33] having produced acute damage of the liver in rats with carbon tetrachloride, found them more susceptible to the quickly acting barbiturates. This susceptibility disappeared after hepatic regeneration. They expressed the opinion that the liver's detoxifying functions are impaired even before cirrhosis develops. Pratt [34] established a close correlation between hepatic function as measured by the bromsulphalein test and the prolongation of the action of soluble pentobarbital U. S. P. (pentobarbital sodium). The action of the barbiturates seems also to be intensified when they are administered in conjunction with morphine to healthy rabbits. Vogeler and Kotzoglu [35] gave rabbits morphine salt in quantities of 0.1 mg. per kilogram of body weight and thirty to forty minutes later induced anesthesia with sodium evipal. These rabbits rested ten times as long as those receiving the same amount of sodium evipal without morphine.

31. Adriani, J.: Fate of Anesthetic Drugs in the Body, Anesthesiology **1**:312-322 (Nov.) 1940.

32. Mousel, L. H., and Lundy, J. S.: Role of the Liver and the Kidneys from the Standpoint of the Anesthetist, Anesthesiology **1**:40-55 (July) 1940.

33. Cameron, G. H., and de Saram, G. S. W.: The Effect of Liver Damage on the Action of Some Barbiturates, J. Path. & Bact. **48**:49-54 (Jan.) 1939.

34. Pratt, T. W., and others: Studies of Liver Function of Dogs, Am. J. Physiol. **102**:148-152 (Oct.) 1932.

35. Vogeler, K., and Kotzoglu, P.: Administration of Morphine Before Inducing Anesthesia by Sodium Evipan, Chirurg **7**:242-245 (April 15) 1935; abstracted, Internat. S. Digest **20**:18-20 (July) 1935.

A comparative study of tests of hepatic function on patients known to have cirrhosis has recently been made at the Los Angeles General Hospital.[1] It would be conservative to say that this group of patients, particularly those who had ascites, had poor hepatic function. Dunlop [36] concluded with regard to the toxicity of procaine that it is inadvisable to use it on patients having severe disease of the liver. He expressed the belief that the liver is not essential for the detoxification of procaine but that it does detoxify procaine more rapidly and efficiently than do other tissues. Even local anesthesia therefore has contraindications in the simple operation of omentopexy.

When portal ascites develops, water metabolism is altered. Many of the factors contributing to diuresis in nephrosis are operative also in patients who have cirrhosis and ascites. It has been accepted that the liver is responsible for the destruction of the short-acting barbiturates and that the barbiturates with more prolonged action, such as barbital and phenobarbital, are excreted by the kidneys. For instance, after bilateral nephrectomy in rabbits, Hirschfelder and Haury [37] found that the depression due to barbital or phenobarbital persisted until death, whereas the shorter-acting barbiturates had little effect. Murphy and Koppanyi [38] produced acute renal lesions in dogs and rabbits with tartaric acid, potassium chromate and uranium acetate. After the administration of barbital to these nephrotic animals there was a reduced concentration of barbital in the urine and a retention of the drug in the blood and tissues. When barbital was given in anesthetic doses the animals failed to survive. Richards and Appel [39] confirmed that when damage to the liver is produced by chloroform or carbon tetrachloride the action of the long-acting barbital is not affected, but there is a marked prolongation of the effect of the shorter-acting group of barbiturates, such as pentobarbital.

CONCLUSION

The prognosis of the patient with cirrhosis seen in this institution is usually poor. Omentopexy performed on selected patients has not prolonged life. The total number of patients in the group who were not treated surgically was 117, and 72 per cent of these patients had died within one year after the onset of symptoms. Fifty-three of this

36. Dunlop, J. G.: The Fate of Procaine in the Dog, J. Pharmacol. & Exper. Therap. **55**:464-481 (Dec.) 1935.

37. Hirschfelder, A. D., and Haury, V. G.: Effect of Nephrectomy on Duration of Action of Barbitals, Proc. Soc. Exper. Biol. & Med. **30**:1059-1060 (May) 1933.

38. Murphy, W. S., and Koppanyi, T.: Studies on Barbiturates, J. Pharmacol. & Exper. Therap. **52**:70-77 (Sept.) 1934.

39. Richards, R. K., and Appel, M.: The Barbiturates and the Liver, Anesth. & Analg. **20**:64-77 (March-April) 1941.

group had ascites and in addition had survived one month after the onset of symptoms. This entire group was treated medically, and 38 per cent of them lived more than one year.

The total number of patients on whom omentopexy was performed for the relief and cure of ascites was 38, and of these 16, or 42 per cent, died within two weeks after the operation. Follow-up study of the remaining patients leads us to conclude that their prognosis is no more satisfactory than it would have been if medical treatment alone had been given.

In the light of the present concept of the formation of ascites the surgical concept that restoration of collateral circulation from the portal system is possibly by mechanical means is false. Only with a sustained elevation of the vascular osmotic pressure will ascites subside, and this, unfortunately, is not as easily achieved in the patient who has cirrhosis as it is in one who has the edema and ascites associated with degenerative nephritis or nephrosis.

The hypoproteinemia of cirrhosis causes important physiologic alterations, all of which are inimical to surgical intervention. The patient is more susceptible to shock; the restoration of fluids subsequent to operation is fraught with serious risk; wound healing is impaired, and the proper administration of any anesthetic is associated with a greater than average danger.

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ACTION OF DIGITALIS ON CONDUCTION IN THE SYNDROME OF SHORT PR INTERVAL AND PROLONGED QRS COMPLEX

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It is stated that the effect of digitalis on the heart can simulate almost every type of electrocardiographic abnormality due to cardiac disorders with the exception of intraventricular conduction defects.[1] As far as the normal electrocardiogram is concerned, this statement is undoubtedly true. The observations of Hart,[2] however, have been widely cited in the literature as indicating that digitalis may occasionally cause a delay in intraventricular conduction and a consequent widening of the QRS complex.

In this study prolongation of the QRS time was produced by digitalis in the course of a clinical experiment. The observations were made in a case of so-called "bundle branch block with short PR interval," a syndrome first observed by Wilson [3] and subsequently described by Wolff, Parkinson and White.[4] Bishop [5] more recently reviewed 45 cases of this syndrome reported in the literature, but as far as we are able to ascertain, the effect of digitalis on this conduction abnormality has not been investigated.

From the Cardiac Service, Sea View Hospital, and the Department of Pharmacology, Cornell University Medical College.

1. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 518.

2. Hart, T. S.: Block of the Branches of the Bundle of His, Arch. Int. Med. **35**:115 (Jan.) 1925.

3. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008 (Dec.) 1915.

4. Wolff, L.; Parkinson, J., and White, P. D.: Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685 (Aug.) 1930.

5. Bishop, L. F.: Bundle Branch Block with Short P-R Interval in Individuals Without Organic Heart Disease, Am. J. M. Sc. **194**:794 (Dec.) 1937.

REPORT OF CLINICAL EXPERIMENT

Clinical Details.—R. G., a Puerto Rican man aged 20, was admitted to Sea View Hospital on March 5, 1940, with pulmonary tuberculosis. There were caseous pneumonic involvement of the entire left lung and a productive lesion in the apex of the right lung (fig. 1). Tuberculosis had been discovered in 1936. In 1936 and 1937 pneumothorax had been induced on each side for several months, and thoracoscopy had also been performed on the left side. There was no history of rheumatic fever, syphilis, hypertension or any cardiovascular symptoms.

Throughout about two years' observation the patient was ambulatory. The general nutrition improved, and the sputum, which had been positive for tubercle bacilli on admission, became negative for such organisms. Examination showed that the heart was displaced to the left, but there was no evidence of cardiac enlargement or of cardiac insufficiency. A pleuropericardial friction rub was heard

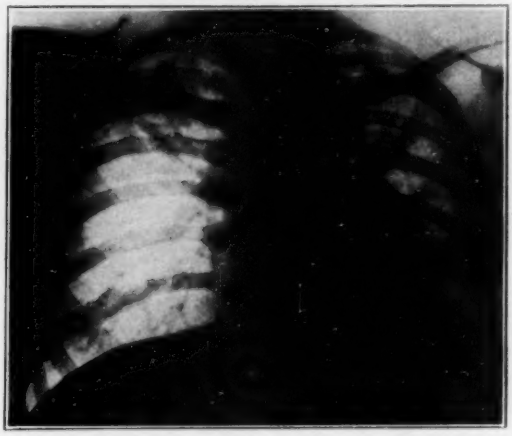

Fig. 1.—A roentgenogram of chest taken on admission. Note the caseous pneumonic involvement of the left lung and a productive lesion in the apex of the right lung, with marked displacement of the heart to the left.

on one occasion. Blood pressure readings fluctuated; the highest was 190 systolic and 90 diastolic, obtained when the patient was first seen; frequently readings of about 130 systolic and 80 diastolic were noted. The radial arteries were barely palpable, and the dorsal pedal arteries were thickened.

The electrocardiogram taken shortly after admission (March 18) showed a short PR interval (0.09 second), abnormal QRS complexes, with a duration of 0.08 to 0.09 second, and abnormal RT segments (fig. 2 *A*).

The second electrocardiogram, taken one month later (April 15), showed a normal record (fig. 2 *B*). On the same day tracings were taken with the patient in several positions and during different phases of respiration: left lateral position, right lateral position and the sitting position, each during both deep inspiration and deep expiration. The only change obtained by varying the conditions in this way was in the height of the R wave in lead I, which was totally abolished in the left lateral position both in deep inspiration and in deep expiration and to a lesser

extent was influenced in other positions. The original abnormal tracing was not reproduced. It seemed likely, therefore, that the abnormal rythm was not the result of mediastinal torsion or displacement.

A tracing taken ten days later (April 25) again showed a short PR interval with abnormal QRS complexes, which differed from the first one in that a notch had appeared on the upstroke of the R wave in lead I near its apex, the R wave in lead II was slurred along the entire upstroke and in lead IV the T wave was positive and there were a reduction in the height of the R wave and a deepening of the S wave. The QRS time was 0.10 second (heart rate 110 per minute). At this time the taking of tracings during deep inspiration and deep expiration (sitting position only) did not introduce any modification of the record.

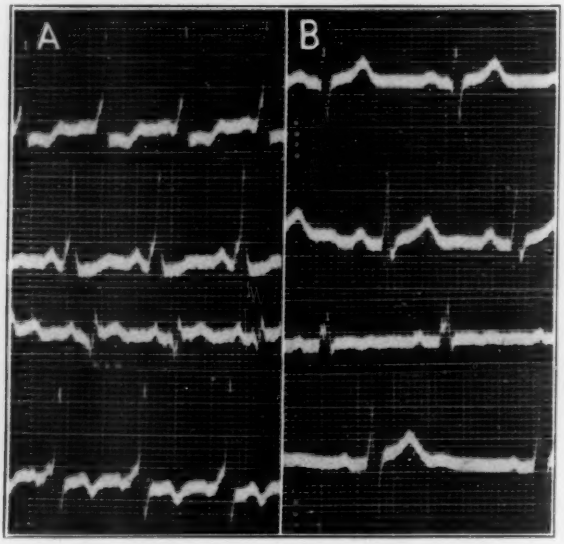

Fig. 2.—*A*, an electrocardiogram taken shortly after admission. Note that the PR interval is 0.09 second and the abnormal QRS complex has a duration of not exceeding 0.09 second. *B*, a tracing taken one month later, showing a normal sinus rhythm. The PR interval measures 0.17 second, and the QRS complexes are normal.

Over ninety electrocardiograms were taken between March 18, 1940 and Jan. 8, 1942. With the exception of the normal tracings obtained on April 15 all showed essentially the same characteristics (figs. 2 *A* and 3 *A*). The QRS time, however, showed a tendency in the later tracings to become prolonged to 0.11 or 0.12 second (fig. 7 *A*).

Several experiments were carried out to determine the effect on the electrocardiogram of changes in vagal tone produced in various ways.

Increased Activity of the Vagus Nerve.—Digitalis: The effect of digitalis on the electrocardiographic syndrome was studied in four experiments. In the first

experiment a dose of 0.4 Gm. of digitalis was given orally on each of three successive days and a tracing (fig. 3*C*) taken on the fourth day (June 3, 1940). At this time the heart rate was slower than in the control records taken before the administration of digitalis (fig. 3*A*). Marked widening of the QRS complex had appeared; after medication with digitalis it was 0.14 second, whereas in the control tracing it was about 0.10 second. The QT interval increased from 0.36 second in the control record to 0.44 second in that taken after medication with digitalis (lead II). This is contrary to observations on the effect of digitalis on the QT interval in regular sinus rhythm.[6]

Three weeks later, after elimination of the drug, the tracing had returned to the appearance of the previous control record. The experiment was then repeated, and a record similar to that in figure 3 *C* was obtained (July 1). Marked prolongation of QRS time by digitalis was observed in two subsequent experiments (fig. 4 *A*). In one of these immediately after a control tracing a single digitalizing dose of digitoxin, 1.25 mg., was given orally and a tracing taken twenty-four

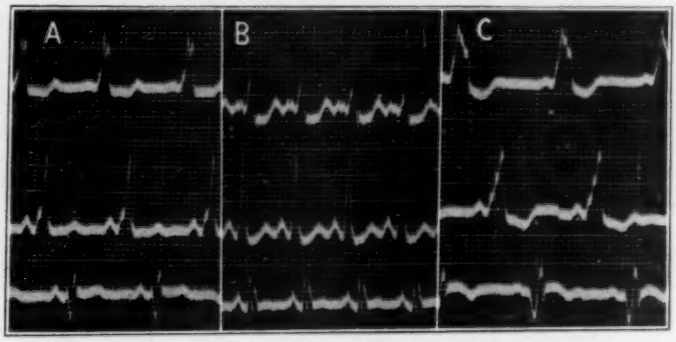

Fig. 3.—The effect of atropine sulfate and of digitalis on the electrocardiographic abnormalities. *A*, the control tracing (May 31, 1940) taken just before the administration of atropine sulfate. *B*, the tracing taken a few minutes after intravenous injection of 2 mg. of atropine sulfate. Note the acceleration of the heart rate from 100 to 150 per minute and decrease in the QRS time from 0.10 to 0.07 second. *C*, the tracing taken on the fourth day (June 3) after beginning administration of digitalis (total dose 18 grains [1.16 Gm.] given orally). Note the slowing of the heart rate from 90 in the control record (*A*) to 70 per minute and widening of the QRS complex to 0.14 second per minute.

hours later. The same effect was observed after the administration of the purified glycoside as after medication with digitalis leaf. Thus, pronounced widening of the QRS complex was produced on each of the four occasions on which digitalis was administered.

6. Cheer, S. N., and Dieuaide, F. R.: Studies on the Electrical Systole ("Q-T" Interval) of the Heart: IV. The Effect of Digitalis on Its Duration in Cardiac Failure, J. Clin. Investigation **11**:1241 (Nov.) 1932.

An arrhythmia (fig. 4 *C*) similar to sinus arrhythmia was frequently seen in the tracings after medication with digitalis.

On December 6, when marked widening of the QRS time was in evidence after the administration of digitalis (fig. 4 *A*), atropine sulfate, 1.2 mg., was given intravenously. The immediate effect (fig. 4 *B*) was an increase in heart rate and a decrease in the QRS time to 0.07 second from the previous value of about 0.14 second. Twenty-four hours later the digitalis effect had reappeared (fig. 4 *C*). At this time the arrhythmia was most distinct. The results of this experiment suggest that the digitalis effect on the QRS complex is vagal in origin.

Pressure on the Carotid Sinus: Pressure on the right and the left carotid sinus had no effect on the electrocardiographic changes (November 29). At this time the control record showed a QRS time of 0.09 to 0.10 second.

Mecholyl Chloride (Acetylbetamethylcholine Hydrochloride): On the same day that the effect of pressure on the carotid sinus was observed 15 mg. of mecholyl chloride was administered subcutaneously. Before administration the blood pressure was 134 systolic and 82 diastolic. Two and one-half minutes after the drug was given,

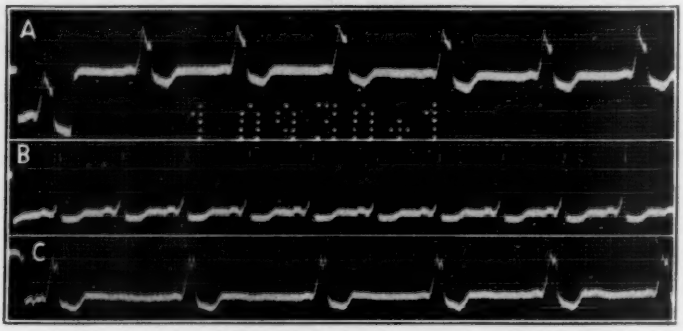

Fig. 4.—The effect of atropine sulfate on the widening of the QRS complex produced by digitalis (lead I). *A*, the tracing taken after digitalization, showing widening of the QRS complex. *B*, the tracing taken immediately after the intravenous injection of 1.2 mg. of atropine sulfate. Note acceleration of the heart rate from 75 to 120 per minute and narrowing of the QRS complex from 0.14 to 0.07 second. *C*, the tracing taken twenty-four hours later, showing reappearance of the digitalis effect on the QRS time and a distinct arrhythmia.

the reading was 126 systolic and 76 diastolic and flushing, lacrimation, sweating and salivation appeared. A tracing was taken at this time and another one ten minutes later, when the blood pressure was 120 systolic and 76 diastolic. The only changes that took place in the electrocardiogram were an increase in heart rate from 95 to 120 per minute and more pronounced notching of the P wave in lead I. This change in the P wave was seen on other occasions when the rate increased (fig. 3 *A* and fig. 3 *B*). Eighteen minutes after mecholyl chloride was administered the heart rate was 110 per minute; the electrocardiogram was not altered in other respects.

Atropine sulfate, 1.2 mg., was then administered intravenously. The sweating, salivation, etc., immediately disappeared, and the blood pressure rose to 152 systolic and 92 diastolic. The electrocardiographic picture changed to a supra-

ventricular type of nodal rhythm (fig. 5), and the QRS complex now resembled that of the normal sinus rhythm (fig. 2*B*). Eight minutes after administration of atropine the tracing had returned to the abnormal form seen in the tracing taken shortly after admission.

Four and a half months later (April 11, 1941) the mecholyl chloride–atropine sulfate experiment was repeated (fig. 6). This time a larger dose of mecholyl chloride, 25 mg., was given subcutaneously. The control blood pressure reading

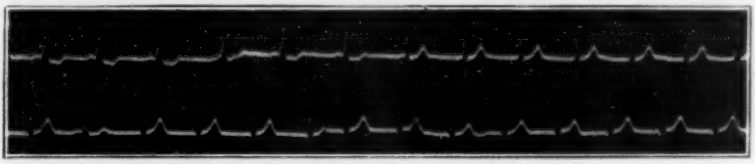

Fig. 5.—The effect of atropine sulfate after the administration of mecholyl chloride (15 mg.), first experiment (lead I). Sections have been selected from a continuous tracing taken immediately after the intravenous injection of 1.2 mg. of atropine sulfate. Note the transition of the electrocardiographic abnormalities to a supraventricular nodal rhythm, with occasional escape to the abnormal form, and occasional appearance of an M-shaped complex.

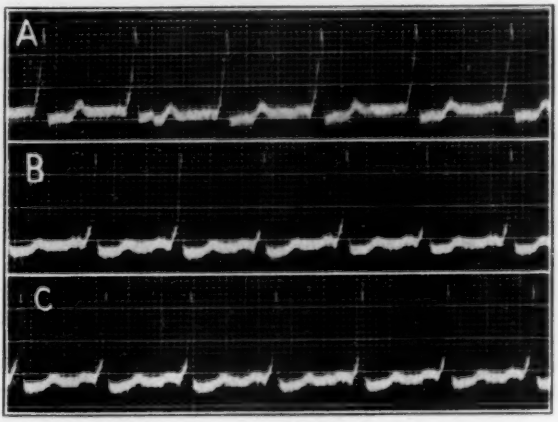

Fig. 6.—The effect of atropine sulfate after the administration of mecholyl chloride (25 mg.), second experiment (lead I). *A*, the control record. *B*, a tracing illustrating the effect of mecholyl chloride. Note that the only changes are a slight increase in rate and more pronounced notching of the P wave. *C*, the tracing taken a few minutes after intravenous injection of 2 mg. of atropine sulfate. The record is the same as that taken after the administration of mecholyl chloride.

was 142 systolic and 80 diastolic. Four minutes after administration of mecholyl chloride it was 134 systolic and 66 diastolic; the patient was flushed, lacrimating and perspiring profusely. Tracings were taken for twelve minutes after the injection. There was no change in the PR interval or in the configuration of the QRS complex (fig. 6*B*). Atropine sulfate, 2 mg., was then injected intravenously.

and tracings were taken for four minutes (fig. 6 *C*). There was no recurrence of the supraventricular type of nodal rhythm.

The appearance of a nodal rhythm in 1 instance after medication with atropine after the administration of mecholyl chloride may be assumed to be due to the asynchronous release of the auriculoventricular node and the sinus node. If the auriculoventricular node is partially released from the influence of the vagus nerve while the sinus node is still relatively under the control of this nerve, a nodal rhythm may appear spontaneously.[7]

Decreased Activity of the Vagus Nerve.—Exercise: Acceleration of the heart rate by exercise had no effect on the electrocardiographic changes.

Atropine Sulfate: This compound, 1.2 mg., was given intravenously (May 6, 1940), and tracings (lead II) were taken immediately and two, four, six, eight and nine minutes later. Resumption of the normal sinus rhythm did not occur. No change in the PR interval was noted. The QRS time decreased from 0.09 second

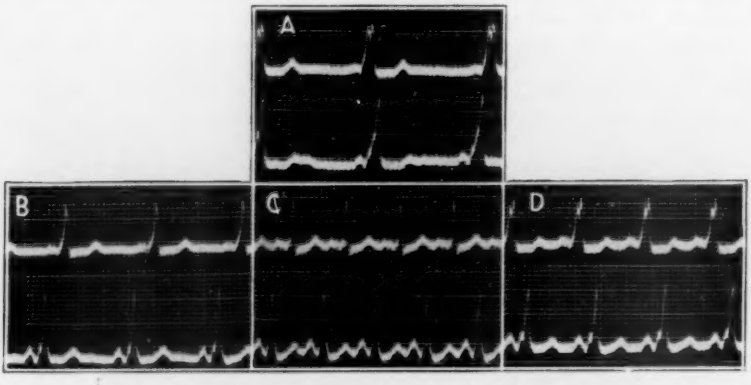

Fig. 7.—Leads I and II are shown. *A*, the tracing taken July 7, 1941, showing spontaneous widening of the QRS complex (QRS time 0.11 to 0.12 second). The other three parts of the figure illustrate the effect of prostigmine methylsulfate on the QRS complex narrowed by atropine sulfate (Aug. 2, 1941). *B*, the control record made before the administration of atropine sulfate. *C*, the effect of atropine sulfate, 2 mg. given intravenously. Note the shortening of the QRS time from 0.09 to 0.05 second in lead I and from 0.10 to 0.08 second in lead II. *D*, the effect of prostigmine methylsulfate, 0.5 mg., given subcutaneously five minutes after the atropine sulfate. Note that the duration of the QRS complex is 0.10 second in lead I and 0.11 second in lead II and thus slightly exceeds that observed in the control record made before the administration of atropine sulfate.

in the control record to 0.07 second after the administration of atropine. The heart rate increased from 100 to 150 per minute.

Subsequently (May 31), a larger dose, 2 mg., of atropine sulfate was administered intravenously. Similar effects were noted, that is, acceleration of the heart

7. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, Arch. Int. Med. **16**:989 (Dec.) 1915.

rate and a decrease in the QRS time to 0.07 second (fig. 3 *A* and *B*). A tracing taken twenty-four hours later resembled the control record taken before the administration of atropine.

The effect of prostigmine methylsulfate following medication with atropine was studied on Aug. 2, 1941. At this time the control tracing (fig. 7 *B*) showed slight spontaneous widening of the QRS complex (heart rate 90 per minute). Atropine sulfate, 2 mg., given intravenously caused acceleration of the heart rate to 140 per minute and marked shortening of the QRS time (fig. 7 *C*). Five minutes later prostigmine methylsulfate, 0.5 mg., was injected subcutaneously. Twenty minutes after the injection of prostigmine, the heart rate had slowed (110 per minute) and the QRS time had lengthened (fig. 7 *D*). It is noteworthy that the QRS time after the administration of prostigmine slightly exceeded that in the control tracing taken before medication with atropine, in spite of the fact that the heart rate was faster.

In the experiments with atropine, mecholyl chloride and digitalis shortening of the QRS time was usually associated with acceleration of the heart rate and widening of the QRS time with a relatively slow rate. That the QRS time is not a function of heart rate is seen by a comparison of selected tracings shown

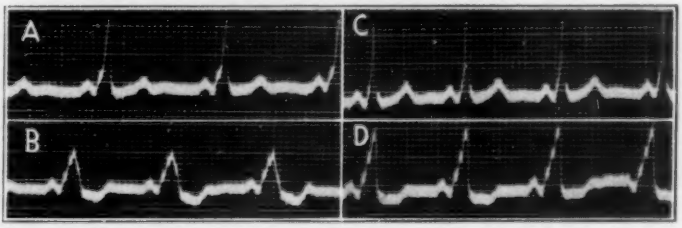

Fig. 8.—Lead II is shown. *A* and *B* compare two tracings in which the heart rate is different. The QRS time in the one with the faster rate (90 per minute) is 0.14 second (*B*), and the one with the slower rate (75 per minute) has a QRS time of 0.10 second (*A*). *C* and *D* show tracings in which the heart rates are essentially the same; the QRS time in one is 0.08 second (*C*) and in the other 0.12 second (*D*).

in figure 8. For instance, tracings with similar rates show widely different QRS durations, and a tracing with a slow rate may have a shorter QRS time than one with a faster rate. Thus, there is no correlation between the heart rate and the width of the QRS complex.

COMMENT

The condition in the case presented is classified as belonging to the syndrome of so-called "bundle branch block with short PR interval." However, it differs from that syndrome as heretofore described in the literature in that the QRS complex associated with the short PR interval was not consistently prolonged. Frequently, particularly in the early tracings, the QRS duration was only 0.09 second. It is possible that this case represents early stages in the evolution of the syndrome.

Opinions differ as to the pathogenesis and the significance of this electrocardiographic picture. The fact that in most instances the abnor-

mality is discovered in the early decades of life, in our case at the age of 20, has suggested that the cause may be a congenital defect of the conduction mechanism. Signs of organic cardiovascular disease are seldom evident in patients exhibiting this syndrome. In the case we have reported, however, the presence of arteriosclerosis and a tendency to hypertension make it impossible to rule out a structural change in the conduction system on an arteriosclerotic basis. In addition, in this case it is conceivable that the extensive tuberculosis may be a factor in the abnormal conduction. It is quite possible, on the other hand, that the arteriosclerotic and tuberculous processes are coincidental, rather than etiologic.

Since it is sometimes possible in this disorder to restore the electrocardiogram to normal by medication with atropine, it is generally believed that the syndrome represents a functional disturbance of conduction which is vagal in origin. In the first case reported,[3] the characteristic electrocardiographic abnormality appeared on stimulation of the vagus nerve and when spontaneously present could be abolished by administration of atropine.

The following theories have been advanced for the mechanism of this syndrome: First, the electrocardiographic abnormality represents nothing more than a nodal rhythm or tachycardia with aberrant conduction in the ventricle.

Here, the cause of aberrant conduction is probably similar to that seen in premature auricular systoles except that the aberrant by-pass remains fixed as long as the impulse arises in the A-V node.[8]

Second, it represents a regular sinus rhythm with functional intraventricular block.[4] Since the start of the QRS complex seems to be responsible for its lengthening and also for the shortening of the PR interval, according to this hypothesis the delay would occur in the upper part of the bundle, and the electrical effect of stimulation of the septum, which is normally recorded as an isoelectric period, would become apparent.[5] Third, the syndrome represents a normal sinus rhythm with conduction by a direct pathway between the sinus node and the ventricle, which results not in a block or delay but in an early arrival of the auricular impulse in the ventricular muscle.[9] This would imply that

8. Katz, L. N.: Electrocardiography, Philadelphia, Lea & Febiger, 1941, p. 524.

9. (*a*) Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent), Am. Heart J. **8**:297 (Feb.) 1933; (*b*) Further Observations on the Production of a Short P-R Interval in Association with Prolongation of the QRS Complex, ibid. **22**:450 (Oct.) 1941; (*c*) Kent, A. F. S.: Some Problems in Cardiac Physiology, Brit. M. J. **2**:105 (July 18) 1914.

the impulse in part passes by way of the "short cut" around the auriculoventricular node and in part travels by the normal pathway.[9a] The hypothesis of aberrant auricular conduction has found experimental proof in the recent work of Butterworth,[10] who short circuited the normal conduction system of the auricle through an amplifier and produced a ventricular asynchronism with the electrocardiographic picture of so-called "bundle branch block with short PR interval." It is clear that under these conditions widening of the QRS complex is not synonymous with intraventricular block.

In the case reported here the results of the experiments with digitalis are in favor of the last hypothesis. Assuming that there are two pathways for the passage of impulses from the sinus node to the ventricles, one by way of the auriculoventricular node and one through the aberrant tissue, whatever depresses the function of the auriculoventricular node will tend further to short circuit auricular conduction, increase the asynchrony of the ventricular responses and lengthen the duration of the QRS complex. The widening of the QRS complex by digitalis would thus result from the well known depressant action of the drug on the auriculoventricular node, causing the impulse from the sinus node to propagate to a greater extent through the aberrant tissue. That this effect of digitalis on the QRS time is vagal is indicated by the fact that the widening is abolished by atropine.

That our patient was susceptible to the influence of the vagus nerve is shown by the slowing of the heart rate and the appearance of an arrhythmia after the administration of digitalis, effects which may be attributable to an action on the sinus node. A more striking demonstration of the role of vagal "tone" is the shortening of QRS time obtained by atropine in each of three experiments. The atropine sulfate-prostigmine methylsulfate experiment also offers additional evidence that the widening of the QRS complex is in this case a function of the vagus nerve. The fact that the widening of the QRS complex following administration of prostigmine slightly exceeded its duration in the control record taken before atropine was administered suggests that prostigmine may have contributed to the inhibition of cholinesterase.

A similar effect of digitalis on the QRS complex associated with a short PR interval has been observed by Scherf and Schönbrunner.[11] It is noteworthy, however, that in this instance the syndrome expressed itself in singly occurring beats rather than as an established rhythm or

10. Butterworth, J. S.: The Experimental Production of the Syndrome of Apparent Bundle Branch Block with Short P-R Interval, J. Clin. Investigation **20**:458 (July) 1941.

11. Scherf, D., and Schönbrunner, E.: Beiträge zum Problem der verkürzten Vorhofkammerleitung, Ztschr. f. klin. Med. **128**:750, 1935.

paroxysm. Their observation that the abnormal beats disappeared after the administration of digitalis is contrary to the findings in our experiment and does not seem to us to justify their conclusion that digitalis has a greater affinity for the aberrant tissue than for the normal auriculoventricular conduction mechanism, since it is possible that the disappearance of the abnormal beats after digitalization may have been related to improvement in myocardial function.

If one accepts either of the first two hypotheses, that the syndrome is essentially a nodal or a sinus rhythm with impairment of intraventricular conduction, one would be forced to conclude that the widening of the QRS complex by digitalis is due to an action on intraventricular conduction. That digitalis ever possesses such an action has not been demonstrated satisfactorily. The evidence of Hart,[2] frequently cited in favor of this action of digitalis, is open to question. In the 2 cases presented by Hart the objections can be raised that there were present organic heart disease and congestive failure, which may of themselves give rise to transitory electrocardiographic changes including bundle branch block and that no data are submitted as to the dose of digitalis, the time of appearance or disappearance of the electrocardiographic change in relation to the medication or the reproduction of the change with repetition of digitalization. Furthermore, the tracings illustrating the effect of digitalis on the QRS complex are not convincing, since in 1 case the widening of QRS time is insignificant (about 0.01 second) and in the other case the QRS configuration following medication with digitalis is so different from that in the control record that it is likely that the rhythm after administration of the drug originates in an ectopic focus (nodal?). This is not an unusual manifestation of the toxicity of digitalis and is due to an action on the pacemaker rather than on intraventricular conduction. Winternitz [12] studied the effect of digitalis on the QRS complex in patients in cardiac failure and observed changes in its amplitude but no prolongation. This is in agreement with general clinical experience.

Not only is there inadequate evidence to establish the existence of a digitalis effect on intraventricular conduction, but there is a lack of satisfactory proof that stimulation of the vagus nerve by other means than medication with digitalis can influence intraventricular conduction. Changes in the ventricular complex during the stimulation of the vagus nerve in dogs were recorded by Hering in 1909,[13] but these applied to

12. Winternitz, M.: Die Digitaliswirkung auf das menschliche Kammerelektrogramm, Ztschr. f. Kreislaufforsch. **23**:452, 1931.

13. Hering, H. E.: Experimentelle Studien am Säugetieren über das Elektrokardiogramm, Arch. f. d. ges. Physiol. **127**:155, 1909.

the amplitude and not to the duration of the QRS complex. Einthoven [14] in 1906 found that stimulation of the vagus nerve in dogs under chloroform anesthesia, which of itself increases vagal tone, did not produce any change in the form or the duration of the QRS complex. Ritchie [15] found that in human subjects likewise stimulation of the vagus nerve never resulted in a prolongation of QRS time, although in 1 instance a lengthening of the "ventricular beat" from 0.35 to 0.45 second was noted; this was at the expense, not of the QRS complex, but of the ST segment and the T wave. We have noted a similar lengthening of the QT interval by digitalis in this case.

The fact that in our case uniform effects were not obtained by the several methods employed to increase vagal activity does not necessarily argue against the correctness of the hypothesis as to the mechanism of the syndrome. For instance, differences in the cardiac response to faradic stimulation of the vagus nerve and to choline derivatives have been demonstrated.[16] It is possible that our patient did not have a sufficiently sensitive carotid sinus and that with respect to mecholyl chloride the dose may not have been large enough.

It is noteworthy that in the later tracings in this case progressive widening of the QRS complex occurred spontaneously and simulated the digitalis effect. This may have a bearing on the evolution of the syndrome and may be assumed to represent progressive depression of the auriculoventricular node with release of the aberrant conduction mechanism. The development of increased vagal tone is also seen in the slowing of the rate concomitant with the spontaneous increase in the QRS time. There was not, however, any constant relation between heart rate and the width of the QRS complex.

SUMMARY AND CONCLUSIONS

A case is reported in which the electrocardiographic picture of short PR interval in association with prolongation of the QRS complex was exhibited. Observations were made over a period of nearly two years.

The effect of changes in vagal activity produced in various ways was studied.

The effect of atropine sulfate on this syndrome was always to shorten the QRS time. This indicates that there was a vagal component in the mechanism of the syndrome.

14. Einthoven, W.: Le télécardiogramme, Arch. internat. de physiol. **4**:132, 1906.

15. Ritchie, W. T.: The Action of the Vagus on the Human Heart, Quart. J. Med. **6**:47 (Oct.) 1912.

16. Starr, I., Jr.: A Note on the Antagonism Between the Cardiac Action of Acetyl-β-Methylcholine and Acetyl Choline, and That of Quinidine, J. Pharmacol. & Exper. Therap. **56**:77 (Jan.) 1936.

In repeated experiments digitalis uniformly produced widening of the abnormal QRS complex. That this effect involves vagal function was demonstrated by its disappearance after administration of atropine.

The results of this study are in harmony with the hypothesis that this syndrome is due to an aberrant conduction mechanism joining the sinal node with one of the ventricles. According to this hypothesis, the widening of the QRS complex by digitalis is due not to an action of the drug on intraventricular conduction, but rather to depression of the auriculoventricular node, resulting in increased activity of the aberrant auricular conduction tissue with consequent increased asynchrony of the ventricular responses.

NOTE: Since this paper was submitted for publication, Butterworth's experiments have been reported in greater detail.[17]

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17. Butterworth, J. S., and Poindexter, C. A.: Short PR Interval Associated with a Prolonged QRS Complex, Arch. Int. Med. **69**:437 (March) 1942.

STORAGE AND SIGNIFICANCE OF TISSUE GLYCOGEN IN HEALTH AND IN DISEASE

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The glycogen in animal tissues has engaged the attention of physiologists since the early work of Claude Bernard. Its significance in health and in disease has also been the subject of scattered observations by clinical investigators since that time. This presentation is an attempt to summarize and correlate such physiologic and clinical aspects of the subject as may be of interest and importance to the practicing physician.

NATURE OF GLYCOGEN

Glycogen is a condensation product, or polymer, of dextrose (*d*-glucose). A molecule of glycogen is composed of twelve units of dextrose, some water being withdrawn in the process of condensation.[1] This product is not peculiar to animal tissue. Starch is similar in its structure and chemistry. However, within the living cell glycogen exists in a characteristic state, which is different from that of glycogen in the chemist's bottle or of starch on the grocer's shelf. In its natural habitat glycogen exists in the colloidal state, the particles of glycogen being composed of large aggregates of glycogen molecules. It seems likely that the colloidal state of the glycogen is preserved by the protective action of certain proteins within the cell.[2]

The physical structure of glycogen may explain the manner in which it is protected from the metabolic activities of the cell which are going on all around it. Carbohydrate is being synthesized and broken down constantly. Under these circumstances the accumulation of more than a small equilibrium amount of glycogen would be difficult to explain from a chemical standpoint were it not for the physical protective barrier of the colloidal state which withholds it from the reaction mixture. This is a phenomenon well known to enzyme chemists. Conversely, the dis-

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From the Department of Metabolism and Endocrinology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.

1. Haworth, J.: Constitution of the Sugars, London, Edward Arnold & Co., 1929.

2. Lazarow, A.: Particulate Glycogen, Science **95**:49, 1942.

appearance of glycogen from the living cell may depend not only on metabolic demands for carbohydrate in excess of the incoming supply but on any injury to the cell which renders the existing conditions unfavorable for the maintenance of the colloidal state and allows the accumulated glycogen to be attacked and dissipated. This may explain in part the known association of good glycogen stores with healthy tissue and the consistently low glycogen levels occurring in diseased tissue. It may also account for the rapid disappearance of glycogen from excised organs and tissues which have been subjected to the trauma of anoxia, handling, etc.

SYNTHESIS OF GLYCOGEN

It must be emphasized from the outset that synthesis of glycogen and breakdown of glycogen are not separate phenomena. They merely represent the opposite directions of the same chemical process. Different glycogen molecules are constantly being built up and broken down at the same time. What is called glycogenesis is merely the net result at any

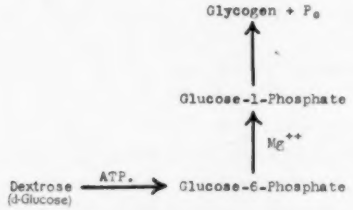

Fig. 1.—The generally accepted scheme of the chemical steps through which dextrose (*d*-glucose) is transformed to glycogen in body tissues.

given time when the rate of formation of glycogen exceeds the rate of breakdown of glycogen. Similarly, glycogenolysis is the net result when the proportionality of the aforementioned rates is reversed. Nevertheless, for purposes of this exposition it will be useful to consider first the factors involved particularly in the synthesis of glycogen.

It is well recognized that the most important precursor of glycogen in the living body is blood sugar. The chemical steps through which dextrose (*d*-glucose) is transformed to glycogen in the tissues have been worked out within recent years, particularly by Cori and his co-workers.[3] The generally accepted scheme is indicated in figure 1. It will be noted that the intermediate steps between dextrose and glycogen all involve phosphorylated compounds. This is a point of fundamental significance, since it is now recognized that the transfer of phosphate

3. Cori, C. F.: Phosphorylation of Glycogen and Glucose, Biol. Symposia **5**: 131, 1941.

groups is the primary means by which the cell derives useful energy from the breakdown of foodstuffs.[4]

In the living animal the transformation of dextrose to glycogen is facilitated by the presence of insulin. The increased deposition of glycogen from dextrose under the influence of insulin, particularly in muscle, is the most firmly established physiologic action of this hormone. However, insulin is not essential to the reaction, since it has been shown that small amounts of glycogen may be deposited in the absence of insulin by the diabetic organism.[5] This fact has received final confirmation from the in vitro work of Cori and co-workers,[3] who have synthesized glyco-

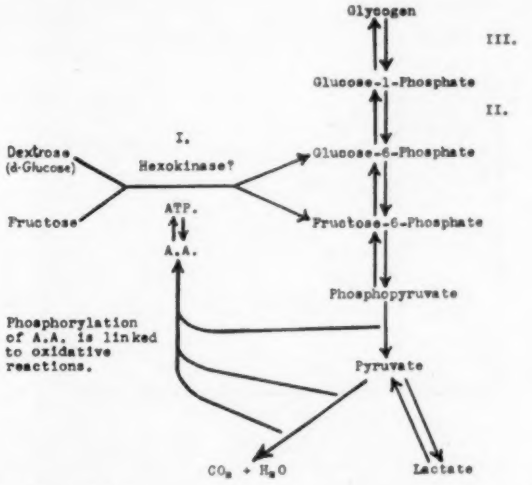

Fig. 2.—The probable manner in which the transformation of dextrose to glycogen is facilitated by insulin. The hormone probably acts at an intermediate step between the hexose phosphates and pyruvic acid and by facilitating certain phosphorylations in this region makes possible the continuous rephosphorylation of adenylic acid (*A. A.*) to adenosine triphosphate (*ATP.*) and thus indirectly increases the rate of phosphorylation of *d*-glucose (dextrose) to glucose-6-phosphate.

gen from dextrose in the test tube in the presence of the necessary enzymes but without insulin. Indeed, they were unable to demonstrate any effect when insulin was added to their system. From this and other evidence it seems unlikely that insulin acts on any of the series of reac-

4. Kalckar, H.: Nature of Energetic Coupling in Biological Syntheses, Chem. Rev. **28**:71, 1941.

5. Major, S. G., and Mann, F. C.: The Formation of Glycogen Following Pancreatectomy, Am. J. Physiol. **102**:409, 1932.

tions indicated in figure. 1. The work of my associates and myself [6] makes it probable that insulin acts at an intermediate step between the hexose phosphates and pyruvic acid, as shown in figure 2. By facilitating certain phosphorylations in this region it makes possible the continuous rephosphorylation of adenylic acid (*A.A.*) to adenosinetriphosphate (*ATP.*) and thus indirectly increases the rate of phosphorylation of *d*-glucose (dextrose) to glucose-6-phosphate.

The major factor other than insulin which determines the rate of synthesis of glycogen is the concentration of sugar present. This is, of course, in accord with the general nature of all enzyme reactions. Cori and Cori [7] have shown that the amount of glycogen deposited in the liver of a given experimental animal depends on the height at which the blood sugar level is maintained, rather than on the total amount of sugar

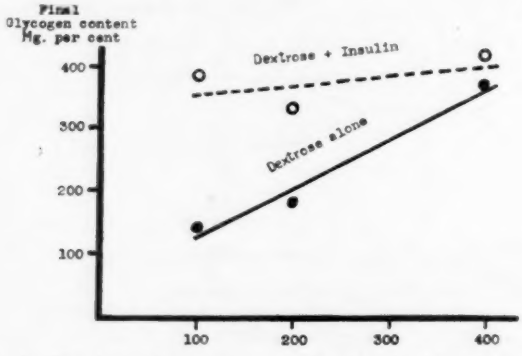

Fig. 3.—The increasing amounts of glycogen deposited in muscle in vitro at increasing concentrations of blood sugar, with and without added insulin.

given. It has been possible in our own laboratory [8] to demonstrate this relation for muscle even more clearly on rat diaphragm in vitro by the Warburg technic. Figure 3 shows the increasing amounts of glycogen deposited at increasing sugar concentrations, with or without added insulin. It will be noted that at the highest concentrations of sugar the

6. (*a*) Soskin, S., and Levine, R.: On the Mode of Action of Insulin, Am. J. Physiol. **129**:782, 1940. (*b*) Levine, R.; Feinstein, R. N., and Soskin, S.: Studies on the Mechansim of Insulin Action in Skeletal Muscle in Vitro, Federation Proc. **1**:50, 1942.

7. Cori, C. F., and Cori, G. T.: The Influence of Insulin and Epinephrine on Glycogen Formation in the Liver, J. Biol. Chem. **85**:275, 1929.

8. Hechter, O.; Levine, R., and Soskin, S.: Relationship Between Sugar Concentration and Glycogenetic Action of Insulin on Rat Diaphragm in Vitro, Proc. Soc. Exper. Biol. & Med. **46**:390, 1941.

insulin did not exert any significant effect in addition to the effect of sugar concentration. It may be stated parenthetically that this relation of the action of insulin to sugar concentration is consistent with other actions which we have been able to demonstrate.[6a] In other words, insulin enables the tissues to do at low or at physiologic concentrations of sugar that for which they would otherwise require high concentrations.

BREAKDOWN OF GLYCOGEN

Since glycogen is the intracellular storage form of carbohydrate, it is the most readily available source of energy for the body. When glyco-

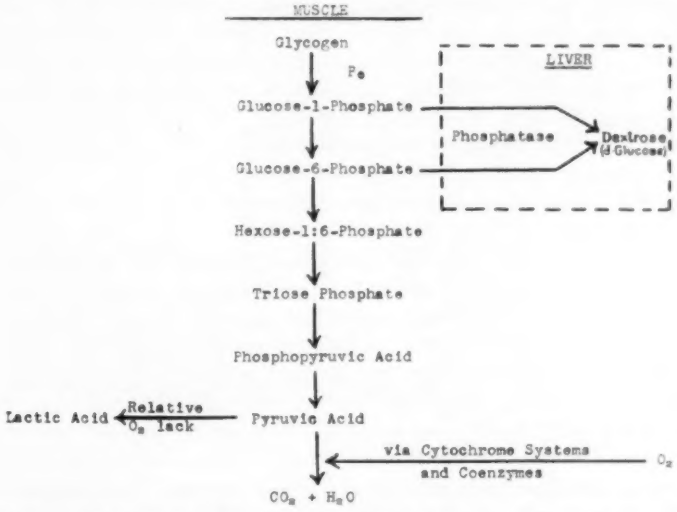

Fig. 4.—The chemical steps involved in the breakdown of glycogen in the muscle and in the liver under ordinary physiologic conditions.

gen breaks down in the muscle under ordinary physiologic conditions, all of it goes through a series of intermediary steps ending in carbon dioxide and water (fig. 4). Lactic acid does not appear under these conditions, and it will be noted from figure 4 that lactic acid is to be regarded as an offshoot from the series of reactions, rather than a direct step in them. The steps from glycogen to pyruvic acid can occur in the absence of oxygen. The steps below pyruvic acid depend on an adequate oxygen supply. When because of an excessively rapid rate of breakdown of glycogen or some impairment in oxygen supply the later steps can no longer keep pace with the early steps, pyruvic acid tends to accumulate. But under these same conditions pyruvic acid is rapidly converted to and appears as lactic acid. Once the disproportion between the rates

at which glycogen is broken down and oxygen is supplied has disappeared, the lactic acid may gradually be oxidized back to pyruvic acid and further to carbon dioxide and water. Meanwhile, however, much of the lactic acid may have diffused out into the blood stream. This lactic acid which appears in the blood under conditions of violent exercise or of relative anoxia is carried to the liver and there reconverted to glycogen. The so-called "lactic acid cycle" is of some significance for the conservation of carbohydrate under conditions of stress and strain but is of no particular importance normally when lactic acid does not pile up in muscle.

Practically all the tissues in the body which have been studied exhibit a pattern of breakdown of glycogen similar to that described for muscle. The liver differs in one respect. This difference does not concern the steps in the direct series of reactions down to carbon dioxide and water but is due to an additional factor which results in the appearance of dextrose as one of the chief end products of breakdown of glycogen. The additional factor is the presence of an active phosphatase which, by splitting the phosphate from hexose phosphates, can divert a large proportion of these intermediate substances from the direct line of degradation.[9]

It will be noted that there is no place in figure 4 for the participation of amylase or glycogenase in the breakdown of glycogen. Such an enzyme was at one time supposed to be responsible for normal glycogenolysis. It now appears that the amylase present in blood is merely an incidental constituent which has diffused out from the parotid and the pancreatic glands. When the liver has been washed free of blood under proper conditions, it is not possible to demonstrate any amylase activity in hepatic tissue. This may be either because the membrane of the hepatic cells excludes the blood amylase or because of the demonstrated fact that there is insufficient chloride ion (Cl^-) within the hepatic cell to allow for amylase activity even if the enzyme could enter. However, under abnormal conditions amylase may assume an important role in breakdown of glycogen. It has recently been demonstrated in our laboratory [10] that the livers removed from animals intoxicated with diphtheria toxin exhibited significant amylase activity within the liver cells. This may explain in part the low levels of liver glycogen in infection and in toxemia, as well as the occurrence of so-called "insulin resistance" under the same conditions. As previously mentioned, insulin probably exerts its influence on the phosphorylating mechanisms involved

9. Cori, C. F.: Glycogen Breakdown and Synthesis in Animal Tissues, Endocrinology **26**:285, 1940.

10. Taubenhaus, M., and Soskin, S.: On the Mechanism of Insulin Resistance in Toxemic States, J. Clin. Endocrinol. **2**:171, 1942.

in glycogenesis. There is no known influence of insulin on the activity of amylase. Hence the intervention of amylase in toxemic states introduces a factor in breakdown of glycogen which cannot be controlled by insulin, regardless of the amounts of insulin administered.

SIGNIFICANCE OF MUSCLE GLYCOGEN

The glycogen within the muscle cells may be reasonably supposed to serve best in emergencies, when the muscle is unable to draw sugar from the blood as quickly as it requires it. But, as a matter of fact, glycogen is more than merely a conveniently packaged form of carbohydrate lying on the pantry shelf. It is now known that more energy is derivable from a certain amount of glycogen than from an equivalent

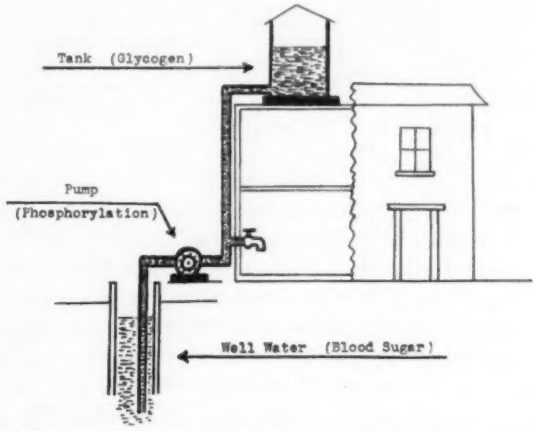

Fig. 5.—A graphic representation of the significance of muscle glycogen, in which the water in the well represents the blood sugar, the pump represents the phosphorylating mechanisms and the tank on the roof represents the store of glycogen.

amount of blood sugar. It requires a certain amount of energy to bring the blood sugar into the metabolic system of the muscle (as hexose-6-phosphate), and therefore all the energy inherent in the dextrose is not available for useful work. On the other hand, the breakdown of glycogen to the same stage does not require the addition of energy and hence makes all its inherent energy quickly available. This is not to say that one gets something for nothing from glycogen, for it required some energy to build up the glycogen in the first place. But this energy was expended during a quiescent period when plenty of it was available. The situation is analogous to that portrayed in figure 5. Here, the water in the well represents the blood sugar, the pump stands for the phosphory-

lating mechanisms and the tank on the roof represents the store of glycogen. It is readily understandable that when the tank contains stored water, the tap can deliver a rate of flow far beyond the rate-capacity of the pump. The water stored during periods when the tap is closed is at a higher level than the original source of the water and also stores some of the energy applied by the pump. This potential energy is released when the tap is opened. Too great an outflow from the tap may, of course, exhaust the stored water and reduce the flow from the tap to the rate at which the pump is capable of operating. A similar situation may occur in muscle, when excessive rates of work over prolonged periods are attempted.

The application of these physiologic facts to clinical phenomena is exemplified by the greater stores of glycogen and of phosphate esters found in the muscles of animals trained to perform prolonged work.[11] This may be related to the physical abilities of manual laborers and of athletes. Conversely, the characteristically low levels of muscle glycogen found in persons with poorly controlled diabetes and in hyperthyroid persons is accompanied by muscular weakness.

The skeletal muscle, to which the foregoing remarks apply, is an organ which must of necessity undertake bursts of exertion. The role of glycogen does not seem to be as important in other organs which characteristically work at more constant rates. For example, the glycogen content of the central nervous system seems to have little significance, for this tissue apparently derives its energy from the blood sugar from moment to moment.[12] Hence its extreme sensitivity to hypoglycemia. The cardiac muscle may be said to occupy a position in between the extremes represented by the central nervous system, on the one hand, and skeletal muscle, on the other. While the heart must vary its output of energy considerably, it does not do so throughout a range comparable to that of skeletal muscle. Its glycogen stores are correspondingly less important. The work of Cruickshank and Kosterlitz [13] has shown that it uses blood dextrose preferentially to glycogen and the latter preferentially to lactic acid However, its stores of glycogen undoubtedly serve it during hypoglycemia, for the heart is not particularly sensitive to this condition. The damaged heart with poor stores of glycogen is more vulnerable. In this condition stenocardial symptoms may be precipitated by a rapid fall of the blood sugar.[14]

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11. Palladin, A.: The Biochemistry of Muscle, Bull. Soc. chim. biol. **13**:13, 1931.

12. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135, 1939.

13. Cruickshank, E. W. H., and Kosterlitz, H. W.: The Utilization of Fat by the Aglycaemic Mammalian Heart, J. Physiol. **99**:208, 1941.

14. Soskin, S.; Katz, L. N.; Strouse, S., and Rubinfeld, S. H.: Treatment of Elderly Diabetic Patients with Cardiovascular Disease: Available Carbohydrate and Blood Sugar Level, Arch. Int. Med. **51**:122 (Jan.) 1933.

SIGNIFICANCE OF LIVER GLYCOGEN

The prime function of the liver in respect to carbohydrate metabolism is to supply sugar to the blood and through this medium to all the other tissues of the body.[15] The rate at which it secretes sugar into the blood is governed by a remarkably efficient homeostatic regulating mechanism which is responsible for the so-called "normal blood sugar level."[16] When sugar is not available from the gastrointestinal tract for any considerable length of time, it must be made by the liver from noncarbohydrate materials. The liver glycogen thus represents a reserve of carbohydrate on which the liver may draw quickly while the gluconeogenetic processes are accelerating to an adequate rate. While this reserve is important for temporary emergencies, it is not always sufficiently appreciated that it represents a rather small amount of carbohydrate, as compared to the body's daily requirements. If one assumes, for example, that a man weighing 70 Kg. with a liver weighing 1,800 Gm. has an average good store of glycogen of about 6 per cent, this would mean a total liver glycogen of 108 Gm. If gluconeogenesis were to cease, this amount of carbohydrate could supply the requirements of his extrahepatic tissues (roughly 0.25 Gm. per kilogram per hour) for about six hours only. The relative importance of the gluconeogenetic processes as compared to the reserve of liver glycogen is obvious.

In view of the foregoing statements it is not surprising that recent work has shown that the anterior lobe of the pituitary gland, the adrenal cortex and the thyroid, as well as the pancreas, exert their important effects on carbohydrate metabolism through the gluconeogenetic processes in the liver.[17] It is beyond the scope of this presentation to go into detail as to the particular effects of these glands. It is important to note, however, that while the anterior lobe of the pituitary, the adrenal cortex and the thyroid all increase the rate of gluconeogenesis in the liver, the activity of none of them results in increased stores of glycogen when there is a relative or an absolute insulin deficiency. It is equally important to remember that the normal animal or human being secretes an optimal amount of insulin for storage of glycogen in the liver. The administration of additional insulin to the normal organism, by causing

15. Soskin, S.: The Liver and Carbohydrate Metabolism, Endocrinology **26**: 297, 1940; The Blood Sugar: Its Origin, Regulation and Utilization, Physiol. Rev. **21**:140, 1941.

16. Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: The Mechanism of Regulation of the Blood Sugar by the Liver, Am. J. Physiol. **124**:558, 1938.

17. Soskin, S.: Metabolic Functions of the Endocrine Glands, Ann. Rev. Physiol. **3**:543, 1941.

a rapid withdrawal of blood sugar into the much bulkier peripheral tissues, results in a greater demand on the liver and an actual lowering of the liver glycogen.[18]

I have previously noted the generally observed association of good stores of glycogen with healthy liver tissue and have suggested that the normal protein structure of the liver cell is essential for glycogen storage. There is considerable evidence that the converse is also true, namely, that good stores of glycogen in the liver cell protect its protein structure. It is possible that the fundamental mechanism may be similar in both instances, that is the preservation of the normal colloidal state. This is merely a speculation, but the fact that glycogen is protective seems certain on an empiric basis.[19] There is ample evidence that hepatic damage due to various injurious agents is minimized in the presence of adequate stores of glycogen. The practical therapeutic application of this knowledge through the use of high carbohydrate treatment is well known.[20] Aside from the possible direct protective action to the hepatic cell, good stores of glycogen may also be necessary for detoxification of the noxious agents coming to the liver. These reactions have recently been studied in vitro. It is known that many such agents are rendered harmless by conjugation with glycuronic acid or by acetylation, both of which processes require the use of carbohydrate by the liver.[21] A lack of available carbohydrate may allow the toxic agents to damage the liver unduly before they are neutralized.

CERTAIN PRACTICAL CONSIDERATIONS

It has been shown that glycogen not only is a storage product which supplies sudden demands for carbohydrate by the body but is a substance which is important for the well-being and the functional intregrity of the tissues. These considerations are particularly important in the treatment of diabetes, in which the lack or the relative lack of insulin interferes with storage of glycogen. It has been an all too common fallacy to assume that a diabetic person has been restored to the normal state because

18. Bridge, E. M.: The Action of Insulin on Glycogen Reserves, Bull. Johns Hopkins Hosp. **62**:408, 1938.

19. (*a*) Soskin, S., and Hyman, M.: Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver, Arch. Int. Med. **64**:1265 (Dec.) 1939. (*b*) Holmes, E.: The Effect of Toxaemia on Metabolism, Physiol. Rev. **19**:439, 1939.

20. Strouse, C. D.; Rosenbaum, E. E.; Levy, R. E., and Soskin, S.: Intensive Carbohydrate Therapy in Diabetic Patients with Manifest or Suspected Liver Disease, J. Clin. Endocrinol. **1**:831, 1941. Soskin and Hyman.[19a]

21. Lipschitz, W. L., and Bueding, E.: Mechanism of the Biological Formation of Conjugated Glucuronic Acids, J. Biol. Chem. **129**:333, 1939. Klein, J. R., and Harris, J. S.: The Acetylation of Sulfanilamide in Vitro, ibid. **124**:613, 1938.

hyperglycemia and glycosuria have been controlled. But this is not necessarily so, unless the means by which the control was accomplished has also led to increased stores of glycogen in the body tissues. From this point of view the use of a substance like decamethylenediguanidine (synthalin), which depresses gluconeogenesis by damaging the liver, is obviously wrong and dangerous regardless of how well it may control the more obvious criteria of diabetes. The high fat diet may be considered to be in the same category, although not nearly so dangerous.

When carbohydrate administration to supplement insulin therapy is advocated for the treatment of diabetic coma, it is often objected that the comatose person is already saturated with sugar, so that the administration of more carbohydrate is useless. A little simple arithmetic will show that this concept is erroneous. The stores of glycogen of such a

Carbohydrate Required to Restore a Comatose Diabetic Person to Normal by the End of the First Twenty-Four Hours of Treatment with Insulin

Subject: A man weighing 70 Kg., with a liver weighing 1,800 Gm., muscle weighing 35 Kg. and 21 liters of blood and extracellular fluid.

	Diabetic Gm.		Normal Gm.	
Liver glycogen	9	(0.5 %)	108	(6.0 %)
Muscle glycogen	70	(0.2 %)	245	(0.7 %)
Extracellular sugar	74	(0.35%)	17	(0.08%)
	153		370	
			153	
Carbohydrate requirement for replenishment of stores, Gm.			217	
Carbohydrate requirement for 24 hour utilization, Gm. (based on 50% of 2,100 calories)			263	
Total, Gm.			480	

person are negligible. The available carbohydrate is chiefly that which is present in the blood. The accompanying calculation clearly shows the inadequacy of his extracellular sugar, as compared to the amount necessary to replenish his stores of glycogen and supply his caloric requirements, as the carbohydrate metabolism reverts to normal under the influence of insulin.

It is evident that almost 500 Gm. of carbohydrate must be administered to this hypothetic person during the first twenty-four hours of treatment and about one half of that amount during subsequent days in order to maintain normal stores of glycogen and carbohydrate metabolism.

The storage and significance of glycogen in health and in disease, while dramatically illustrated in diabetic patients, is sufficiently important in patients suffering from other conditions and in normal persons to merit careful attention at all times.

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MORPHOLOGY OF ERYTHROCYTES IN ERYTHROBLASTOSIS FOETALIS

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Acute hemolytic anemias due to autoantibody reactions have been observed in human beings [1] and induced experimentally in animals.[2] Hematologic examination of the experimental animals has revealed a fairly consistent pattern of morphologic change. During the initial phase of hemolysis, the mean cell diameter decreases and the mean cell volume increases, the cells assuming a spheroid shape. After several days the mean diameter rises above normal with the simultaneous appearance of macrocytes, nucleated red cells and increased numbers of reticulocytes. At this time the Price-Jones curve is frequently bimodal, and Dameshek has stressed this point as being of diagnostic import in such anemias.

The recent work of Levine and his associates [3] has shown that about 90 per cent of infants with erythroblastosis foetalis have an antigen, designated as Rh, in their blood cells which is inherited from the father, probably as a mendelian dominant character, and which the mother

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1. (*a*) Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231, 1940; (*b*) The Presence of Hemolysins in Acute Hemolytic Anemia: Preliminary Note, New England J. Med. **218**:75, 1938. (*c*) Farrar, G. E.; Burnett, W. E., and Steigman, A. J.: Hemolysinic Anemia and Hepatic Degeneration Cured by Splenectomy, Am. J. M. Sc. **200**:164, 1940. (*d*) Reisner, E. H., Jr., and Kalkstein, M.: Autohemolysinic Anemia with Auto-Agglutination: Report of a Case with Splenectomy, ibid. **203**:313, 1942.

2. (*a*) Price-Jones, C.: The Variation in the Sizes of Red Blood Cells, Brit. M. J. **2**:418, 1910. (*b*) Passey, R. D., and Braine, J. F. C.: Variations in the Size of the Red Cells in Some Experimental Anaemias in Rabbits, Guy's Hosp. Rep. **74**:217, 1924. (*c*) Filo, E.: Anémies hémolytiques provoquées par le sérum érythrolytique, Sang **10**:178, 1936. (*d*) Dameshek, W., and Schwartz, S. O.: Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, Am. J. M. Sc. **196**:769, 1938. (*e*) Tigertt, W. D., and Duncan, C. N.: Erythrocyte Morphology in Experimental Hemolytic Anemia as Induced by Specific Hemolysin, ibid. **200**:173, 1940. (*f*) Whipple, A. O.: Observations on the Function of the Spleen with Reference to the Familial Hemolytic Anemias, paper read at the meeting of the New York Academy of Medicine, Section of Surgery, Feb. 6, 1942.

3. Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**:925, 1941.

lacks. With the demonstration of anti-Rh antibodies in the serum of a large percentage of the mothers of erythroblastotic infants the plausible hypothesis was advanced that erythroblastosis foetalis is the result of an intrauterine antigen-antibody reaction.[4] Further work has shown that an additional 7 per cent of erythroblastotic infants have mothers whose blood contains Rh antigen but who lack a genetically related antigen designated hR, which the babies have. It seems likely that eventually all cases of erythroblastosis may be shown to depend on these or similar factors.

In the light of the foregoing facts this study was undertaken to determine to what extent the blood picture in erythroblastosis foetalis simulates the picture seen in experimental anemias due to autoantibodies.

METHOD AND MATERIAL

Records and blood smears in 24 cases of fetal hydrops and of icterus gravis neonatorum were studied. In 7 cases these were personally obtained, and in the remainder they were obtained through Dr. Carl T. Javert, of the Department of Obstetrics, and Dr. Carl Smith, of the Department of Pediatrics.

The smears obtained from the obstetric service were all of cord blood drawn at birth from the umbilical vein; the others were of peripheral blood obtained by finger prick or heel prick. All smears were stained by the usual Romanowsky technic. Hemoglobin determinations were made by the Sahli-Hellige method. Red cell counts were made with red cell pipets standardized by the United States Bureau of Standards. Reticulocytes were stained in vivo with 0.5 per cent brilliant cresyl blue and the number of reticulocytes per five hundred red cells counted in dried smears counterstained with Romanowsky stains (Hastings' stain or Wright's stain).

Price-Jones curves were made by the direct measurement of the diameters of three hundred consecutive round cells in dried smears with an ocular micrometer scale calibrated to measure to 0.7 micron. Fields were selected where the cells were not in contact with each other, where they were uniformly distributed and where there was a minimum of distortion of their outlines. At the outset of the study several curves were done by different observers as a check. In the cases which came under personal observation curves were made at frequent intervals until the blood picture had returned to normal. In several instances when the figures obtained from counting three hundred cells seemed open to question an additional three hundred cells were counted and the total figures divided by 2.

For controls, smears of cord blood taken at birth and peripheral blood taken four hours after birth were made on 5 normal newborn infants of mature weight (more than 2,500 Gm.) and the diameters of three hundred consecutive round cells per smear counted. The combined results for the three thousand cells were reduced to a scale of three hundred cells for comparison. Red cell counts and hemoglobin determinations were also made. In addition, Price-Jones curves were

4. This hypothesis had been previously advanced by Darrow (Icterus Gravis [Erythroblastosis] Neonatorum: Examination of Etiologic Considerations, Arch. Path. **25**:378 [March] 1938) on the basis of the clinical and pathologic evidence but with no knowledge of the specific antibodies involved.

made for 12 infants between the ages of 2 hours and 1 month suffering from prematurity and diarrhea (2), intracranial hemorrhage (2), asphyxia neonatorum (2), pyloric stenosis (1), pylorospasm (1), infection (3) and obstructive jaundice (1). Several of these infants (fig. 9) had marked anemia. In 2 instances Price-Jones curves for three hundred consecutive reticulocytes were made.

In 600 cases of marked erythroblastemia differential counts were made on one hundred consecutive nucleated red cells. The cells were identified according to the classification advocated by Dameshek and Valentine[5] and Jones,[6] slightly modified as follows:

Proerythroblast: This type of cell is large, with deeply basophilic cytoplasm containing one or more vacuoles and a lighter nucleus filling most of the cell, in which the chromatin is arranged in a uniform, scroll-like pattern, with several nucleoli.

Megaloblast A: Only slightly smaller than the preceding cell, this type has a basophilic cytoplasm and a nucleus in which the chromatin is still scroll-like in character.

Megaloblast B: In this cell the cytoplasm is polychromatic and the nucleus is smaller. The nuclear chromatin is clumped in coarse strands like a ball of yarn but is still less clumped than that in the corresponding cell of the normoblast series.

Normoblast A: The cytoplasm resembles that of megaloblast A, but the cell is slightly smaller, and the nuclear chromatin shows definite clumping.

Normoblast B.: The cytoplasm is polychromatic, and the nucleus shows a definite pattern of clumping, often resembling the spokes of a wheel (*Radkern*) or a clock face.

Orthochromatic mixed group: Since in the final stages of maturation it is often impossible to differentiate normoblasts and megaloblasts from each other, all orthochromatic nucleated red cells with pyknotic nuclei were arbitrarily placed in this group.

For the sake of consistency all patients who exhibited even a small amount of edema were classified as having fetal hydrops and the remainder as having icterus gravis, except for 1 infant (baby TH.), who exhibited neither edema nor icterus and is listed as unclassified.

RESULTS

There were 12 cases of fetal hydrops; in 5 cases the infants were stillborn, in 4 they died shortly after birth and in 3 they recovered. In all cases the Price-Jones curve was bimodal at the time of the first examination of the blood. In 6 instances the peaks were at 8.4 and 9.8 microns. As can be seen from table 1, in all these cases the condition

5. Dameshek, W., and Valentine, E.: The Sternal Marrow in Pernicious Anemia: Correlation of Observations at Biopsy with Blood Picture and Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, Arch. Path. **23**:159 (Feb.) 1937.

6. Jones, O. P.: Cytology of Pathologic Marrow Cells with Special Reference to Bone Marrow Biopsies, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2045.

was severe, and the infants either were stillborn or died shortly after birth. The curves of the remaining 6 infants showed peaks at 7.0 and 8.4 microns (fig. 1).

There were 11 cases of icterus gravis; in 3 cases the infants were stillborn, in 1 death occurred at four days and in 7 the infants recovered. One unclassified baby died the day after birth. Of these 12 patients, 10 showed a bimodal curve at 7.0 and 8.4 microns on the initial examination of the blood, and for 1 such a curve developed on the third day of

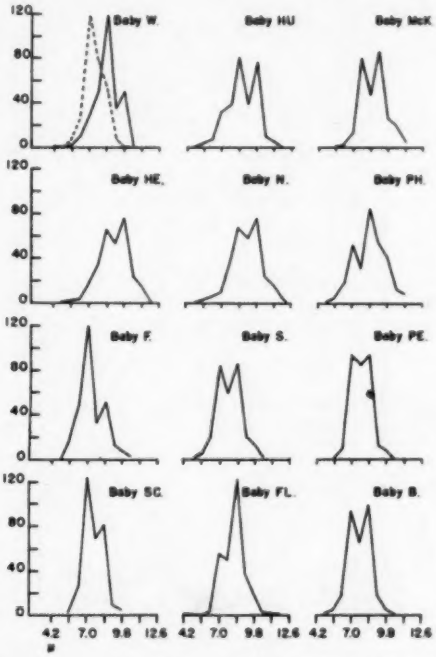

Fig. 1.—Price-Jones curves (three hundred cells each) made on 12 infants with fetal hydrops. (The dash line is a control curve.)

life (case 5, baby I.). The curve for 1 (case 1, baby D.) was monophasic with a microcytic peak at 5.6 microns. This patient did not come under personal observation, so it was unknown whether a bimodal curve developed later, but a smear of blood taken after recovery was essentially normal (table 2 and fig. 2).

In the 5 infants observed until recovery a definite pattern can be demonstrated (figs. 3 through 7). Both baby B. (case 3, fig. 3) and

TABLE 1.—*Pertinent Data on the Blood of Twelve Infants with Fetal Hydrops* *

Baby	Hemoglobin, Gm./100 Cc.	Erythrocytes, Millions/Cu. Mm.	Nucleated Red Cells/100 White Cells	Red Cell Diameters, μ 300 Consecutive Round Cells												Outcome and Changes Noted in Liver at Necropsy
				4.2	4.9	5.6	6.3	7.0	7.7	8.4	9.1	9.8	10.5	11.2	11.9	12.6	
W.*	...	....	328	1	..	3	9	30	49	121	35	49	2	1	..	..	Stillborn; dense hemopoietic foci
HU.	4.5	1.00	686	..	2	5	8	32	38	82	40	77	10	6	3	1	Died 15 min. after birth; no necropsy
McK.*	...	....	1,086	..	..	1	4	14	19	81	47	86	28	19	6	..	Stillborn; no necropsy
HE.*	2.0	0.50	204	..	2	3	4	17	35	66	55	76	24	16	2	..	Stillborn; numerous hemopoietic foci
N.*	2.8	0.57	140	1	..	4	7	10	35	69	59	76	25	17	5	1	Stillborn; many hemopoietic foci; fibrosis
PH.*	4.6	1.27	980	..	..	1	2	6	17	52	31	85	53	42	13	9	Died; hemopoietic foci; bile pigment, fibrosis
F.*	....	....	166	..	1	18	51	120	34	51	13	8	4	..	..	..	Died; many hemopoietic foci; iron pigment
S.	22.8	6.00	102	..	2	7	21	84	69	86	22	14	3	1	..	..	Recovered
PE.*	....	....	190	..	..	2	10	95	85	95	17	10	2	..	..	..	Stillborn; hemopoietic foci
SC.	13.6	4.80	370	..	..	4	27	122	69	83	11	7	..	..	..	..	Died 2 hr. after birth; no necropsy
FL.	16.0	4.20	214	1	1	..	5	56	51	121	38	20	4	1	1	..	Recovered
B.	12.0	4.00	54	..	2	5	18	93	67	100	19	7	1	..	..	..	Recovered

* Six hundred cells were counted.

baby FL. (case 4, fig. 4) showed a definite perponderance of macrocytes at the outset but with appreciable numbers of normal-sized cells. As recovery progressed clinically, accompanied by the decrease in numbers of nucleated red cells, the proportion of macrocytes decreased and that of normocytes increased, the curve becoming first plateau shaped on the right side and then monoapical. With baby I. (case 5, fig. 5) the number of macrocytes was so great that only a slight broadening of the base of the curve indicated the presence of normocytes on the first day of life,

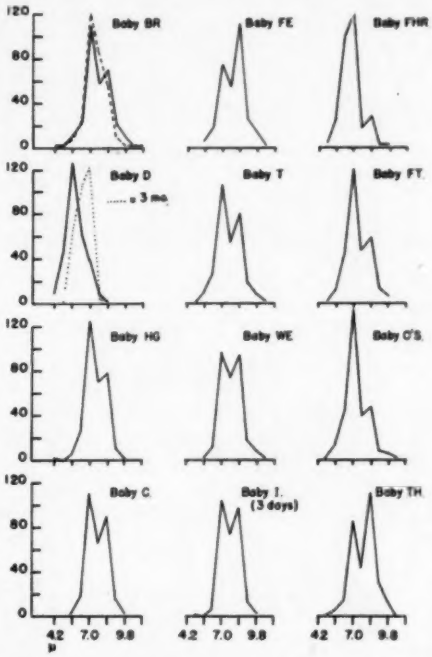

Fig. 2.—Price-Jones curves made on 11 infants with icterus gravis and 1 infant with unclassified erythroblastosis foetalis (baby TH.). The dash line is a control curve.)

and on the second day a symmetric macrocytic curve appeared. On the succeeding day, however, there was a marked increase in the number of normocytes, and the curve became first biphasic and then monophasic and was well on the way to normal by the seventh day. Baby FT. (case 6, fig. 6) was not so sick as the others, and in his case the rapid restoration of a normal curve, slightly on the microcytic side, is seen by the end of a week. Baby WE. (case 7, fig. 7) showed a bimodal curve at the outset, with rapid increase of macrocytes and a gradual return toward

TABLE 2.—*Pertinent Data on the Blood of Eleven Infants with Icterus Gravis and One Unclassified Infant*

Baby	Hemoglobin, Gm./100 Cc.	Erythrocytes, Millions/Cu. Mm.	Nucleated Red Cells/100 White Cells	Red Cell Diameters, μ 300 Consecutive Round Cells												Outcome and Changes Noted in Liver at Necropsy
				4.2	4.9	5.6	6.3	7.0	7.7	8.4	9.1	9.8	10.5	11.2	11.9	12.6	
BB.	....	....	98	1	2	9	22	108	57	70	20	11	1	1	..	..	Stillborn; hemopoietic foci
FE.	14.0	3.90	52	..	..	7	19	71	53	110	26	15	1	..	..	..	Stillborn; hemopoietic foci
FHR.	6.0	1.40	255	..	4	27	100	121	18	27	3	1	..	..	..	..	Recovered
D.*	10.8	3.10	6	9	48	130	63	40	9	1	..	..	..	..	..	..	Recovered
3 mo. later	....	....	0	..	3	66	105	122	5	1	..	..	..	..	..	..	Recovered
T.	16.5	5.30	40	..	1	10	25	105	55	80	17	8	1	..	..	..	Recovered
FT.	18.5	6.50	28	..	3	12	44	120	47	57	12	7	..	..	..	..	Recovered
HG.	17.1	7.00	47	1	..	6	26	125	72	78	11	3	..	..	..	..	Stillborn; numerous hemopoietic foci
WE.	17.5	5.00	50	..	..	2	12	97	75	94	19	8	1	..	..	..	Recovered
O'S.*	7.3	1.30	362	..	1	15	45	138	40	45	8	6	2	..	..	..	Recovered
C.	13.0	2.70	5	..	..	1	18	110	67	90	16	4	..	..	..	..	Died 3rd day; numerous hemopoietic foci
I. (3rd day)	13.2	3.52	14	..	1	1	7	103	73	96	15	4	..	..	..	..	Recovered
TH.	20.0	6.30	500	..	1	6	14	84	48	110	31	15	2	..	..	..	Died 1st day; marked necrosis of liver

* Six hundred cells were counted.

normal. A sixth infant, baby C. (case 8, fig. 8), was observed until death, which occurred on the third day of life. His curve was biphasic at first but then shifted to the left after a transfusion. Simultaneously, he became more icteric, and the blood count failed to rise. The clinical

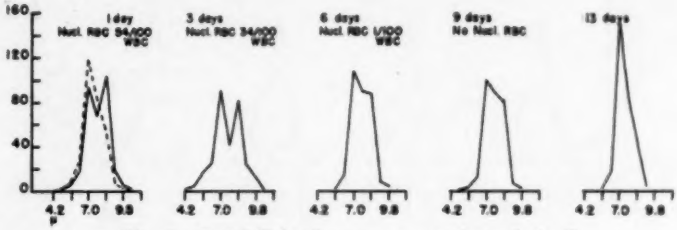

Fig. 3.—Serial Price-Jones curves made on baby B.

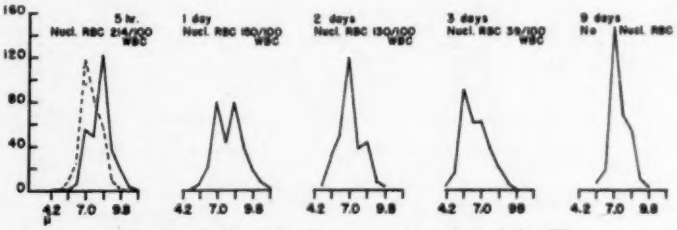

Fig. 4.—Serial Price-Jones curves made on baby FL.

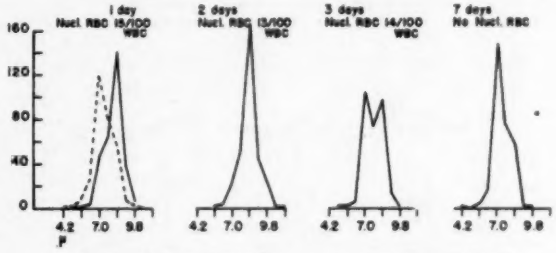

Fig. 5.—Serial Price-Jones curves made on baby I.

picture was that of increased hemolysis, of which the leftward shift of the curve was also an indication.

The control studies showed an average red cell count on cord blood of 5,078,000 and an average hemoglobin level of 15.6 Gm. per hundred cubic centimeters, as compared with values of 6,134,000 and 20.3 Gm., respectively, obtained on the same infants four hours later. This marked difference was attributed to dehydration. The Price-Jones

curve for the whole group (three thousand cells) was monoapical, with a definite broadening of the base. Curves done on combined cord blood smears and peripheral blood smears coincided closely. The mean cell

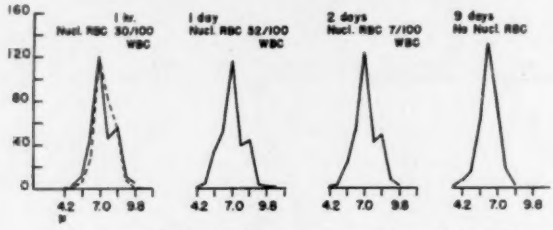

Fig. 6.—Serial Price-Jones curves made on baby FT.

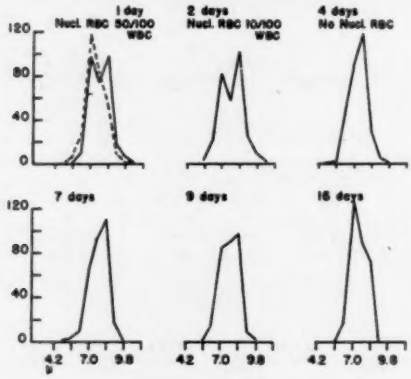

Fig. 7.—Serial Price-Jones curves made on baby WE.

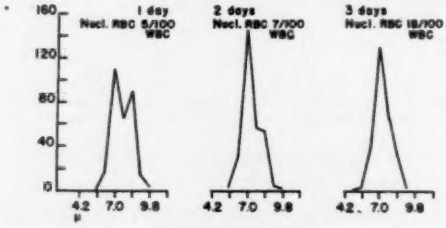

Fig. 8.—Serial Price-Jones curves made on baby C.

diameter for the three thousand cells was 7.44 microns, which coincides closely with Silvette's figure of 7.45 microns,[7] for six thousand cells in

7. Silvette, H.: A Study of Erythrocyte Diameters in the Newborn, J. Lab. & Clin. Med. **13**:245, 1927.

30 babies less than 48 hours old, and is less than van Creveld's figure of 8.0 microns.[8] The mean cell diameter of the cord blood was 7.47 microns and of the peripheral blood 7.41 microns.

In the 12 control curves (fig. 9), although several of the patients showed marked anisocytosis, the distribution was usually fairly uniform, and in no case was the curve biphasic.

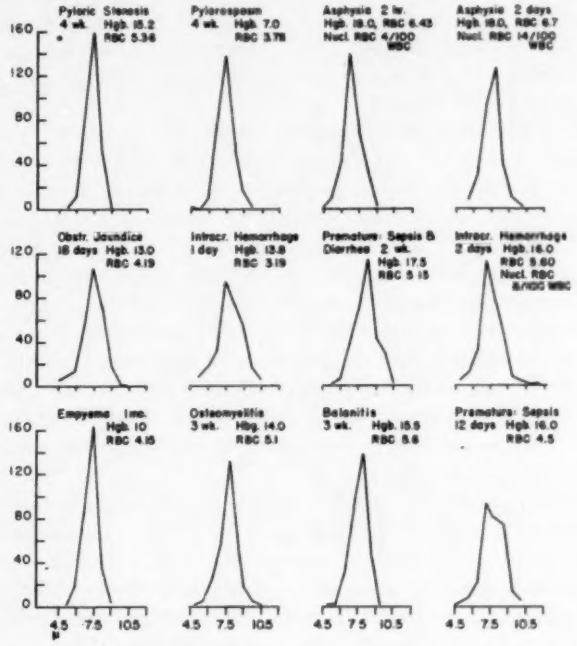

Fig. 9.—Price-Jones curves made on 12 infants aged 2 hours to 1 month, suffering from a variety of conditions.

COMMENT

From the foregoing material it became evident that patients with erythoblastosis exhibited morphologic alterations in the red cells of the same general type as those seen in clinical and in experimental autohemolytic anemias. In 23 cases the Price-Jones curves were biphasic with macrocytic peaks, and in 1 case (1, baby D.) there was marked microcytosis. The case record of this patient aids in interpreting this curve (see appended case reports.)

8. van Creveld, S.: Diameter of Red Blood Cells of Premature Infants and of Those Born at Full Term, Am. J. Dis. Child. **44**:701 (Oct.) 1932.

The true nature of the illness of baby D. was brought out by the transfusion with paternal blood, which, in the light of present knowledge, probably contained antigens against which the infant's blood had antibodies, transmitted to it diaplacentally by the mother. The resulting hemolysis was attested to by the fall in blood count and the rise in icteric index after transfusion. At this time (Oct. 3, 1937) the Price-Jones curve showed a marked shift to the left (fig. 2). The mean cell volume at the same time was 109.8 cubic microns, from which one may conclude that the cells were smaller and rounder, and the smear revealed the presence of spherical microcytes with hyperchromatic centers in contrast to the central pallor of the normal erythrocytes present. Spherocytes are more fragile in hypotonic solution of sodium chloride, and this is reflected in the results of fragility tests done on this patient. Whipple [2f] has recently shown that the cause of splenic enlargement in experimental hemolytic anemia in animals is that the spherocytes, because of their increased volume, cannot pass through the stomas of the splenic venous sinuses freely. This may explain the marked splenomegaly suddenly appearing at this time in this patient. Finally, when another donor was used, the patient made a gradual recovery and at the end of three months had a normal red cell diameter, blood count, icteric index and red cell fragility. From these facts the possibility of this being a case of familial hemolytic icterus seems definitely excluded. Whether the pathologic cerebral condition later uncovered was in any way related to the icterus gravis is pure speculation in the absence of autopsy evidence of nuclear bile staining (kernikterus).

Any natural property of a homogeneous population can be expressed as a function of two dependent variables, x = (f) y. This gives a simple binomial curve in the shape of a parabola. The more cells one counts the closer the observed curve will coincide with the expected curve of variation. When the observed curve, however, coincides only slightly or not at all with the expected curve, one may assume that one is dealing with a heterogeneous population. Thus, the foregoing observations indicate the presence of three races of cells, each following a homogeneous pattern: e. g. microcytes, normocytes and macrocytes. Obviously, to speak of a mean cell diameter in such a group is meaningless.[9]

In analyzing the macrocytic curves more closely the main question was the nature of the macrocytes. The accepted view is that they are reticulocytes and immature cells which are called forth in response to destruction of blood.[10] Reticulocytes are known to be about 1 micron

9. Price-Jones, C.: The Diameters of Red Cells in Pernicious Anemia and in Anemia Following Hemorrhage, J. Path. & Bact. **22**:487, 1922.

10. Wintrobe, M. M.: Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia, J. Clin. Investigation **13**:669, 1934. Dameshek and Schwartz.[1a] Tigertt and Duncan.[2e]

larger than the red cells into which they mature,[11] and undoubtedly they account for part of the macrocytic cells in the present cases. However, there is a wide discrepancy between the number of macrocytes predictable from the reticulocyte percentage plus the normal expectancy, and the actual numbers. For example, in the curve illustrated in figure 10 *B* the reticulocyte percentage was 6.7, or twenty of three hundred cells. The expected number of red cells 8.4 microns in diameter in a homogeneous cell population of normal mean diameter has not been calculated. However, it can be readily seen that it should be such that when added to the number of reticulocytes the total number of cells 8.4 microns in diameter would be far less than that observed, ninety.

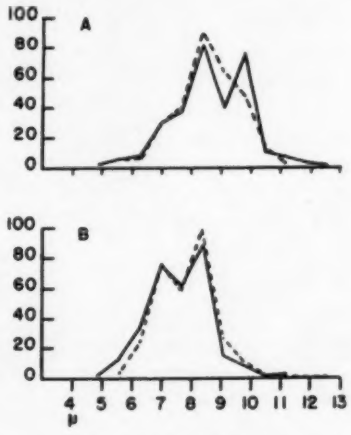

Fig. 10.—Price-Jones curves (three hundred cells each) made on erythrocytes (solid line) and reticulocytes (dotted line) of 2 infants with erythroblastosis foetalis.

Moreover, if the macrocytosis is due to reticulocytes, distribution curves done on reticulocytes should show more macrocytosis than those done on mature red cells. Therefore, on two smears available in which the reticulocytes were sufficiently numerous to count, such comparative Price-Jones curves were made in the usual fashion. The results (fig. 10 *A* and *B*) show that the reticulocytes do not follow the anticipated distribution. It is likely that in some of the milder cases with small macrocytic peaks the peaks represent reticulocytes, but in more severe cases another explanation must be sought.

11. Persons, E. L.: Studies of Red Blood Cell Diameter: III. The Relative Diameter of Immature (Reticulocytes) and Adult Red Blood Cells in Health and Anemia, Especially in Pernicious Anemia, J. Clin. Investigation **9**:615, 1929.

The degree of reticulocytosis in erythroblastosis foetalis reported by different authors varies. In Diamond, Blackfan and Baty's [12] series it was 8 to 20 per cent; Hawksley and Lightwood [13] reported figures ranging between 3 and 11.9 per cent on the initial smear; Vogel [14] reported 5 to 30 per cent, and in the cases reported by Javert [15] it averaged 7.1 per cent. It appears that the degree of reticulocytosis is not as high as one usually encounters in other hemolytic anemias with a comparable degree of blood destruction, and the possibility of marrow inhibition must be considered. In the presence of macrocytosis the cause of inhibition might theoretically be a lack of the erythrocyte maturation factor stored in the liver.

To investigate this point differential counts were made on the nucleated red cells in the smears of 6 patients with severe erythro-

TABLE 3.—*Differential Counts for Nucleated Red Cells (One Hundred Cells) for Six Infants with Severe, Fatal Erythroblastosis Foetalis*

Baby	Hemoglobin, Gm./100 Cc.	Erythrocytes, Millions/ Cu. Mm.	Nucleated Red Cells/100 White Cells	Proerythroblast	Megaloblast A	Megaloblast B	Normoblast A	Normoblast B	Orthochromatic Mixed Group	Changes Noted in Liver at Necropsy
W.....	...	....	328	..	1	22	1	22	54	Densely packed hemopoietic foci
F.....	...	....	166	2	4	7	1	9	77	Many hemopoietic foci; brown pigment
HE.....	2.0	0.50	204	2	10	16	8	10	54	Numerous hemopoietic foci
TH.....	20.0	6.30	500	3	8	13	4	10	62	Extensive hemorrhagic necrosis; hemopoiesis
HU.....	4.5	1.00	686	3	3	14	13	16	50	No autopsy
McK.....	...	....	1,686	3	10	12	7	21	47	No autopsy

blastosis, all of whom died. The results have been tabulated (table 3). In all cases unmistakable megaloblasts were observed (fig.11). Four of the 6 patients were examined at autopsy, and all of them showed varying degrees of hepatic damage, ranging from crowding of the hepatic parenchyma by extramedullary hemopoietic centers to extensive hemorrhagic necrosis (fig. 12), cellular infiltration, fibrosis and heavy deposits of iron and of bile pigment.

12. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, J. Pediat. **1**:269, 1932.

13. Hawksley, J. C., and Lightwood, R.: A Contribution to the Study of Erythroblastosis: Icterus Gravis Neonatorum, Quart. J. Med. **27**:155, 1934.

14. Vogel, P.: Clinical and Hematological Aspects of Erythroblastosis Fetalis, read at a meeting of the New York Pathological Society, New York Academy of Medicine, Jan. 22, 1942.

15. Javert, C. T.: Erythroblastosis Neonatorum, Surg., Gynec. & Obst. **74**:1, 1942.

The significance of megaloblasts is still a subject of controversy, but at present a majority of investigators in this country and Europe incline to the opinion that they represent an abnormal type of erythropoiesis which occurs in the absence of the hepatic erythrocyte maturation factor.[16] The presence of megaloblasts in these smears may similarly point to hepatic insufficiency as the major contributory cause of the macrocytosis in the cases with high macrocytic peaks. This is not unexpected in view of the many other evidences of hepatic damage in erythroblastosis foetalis.

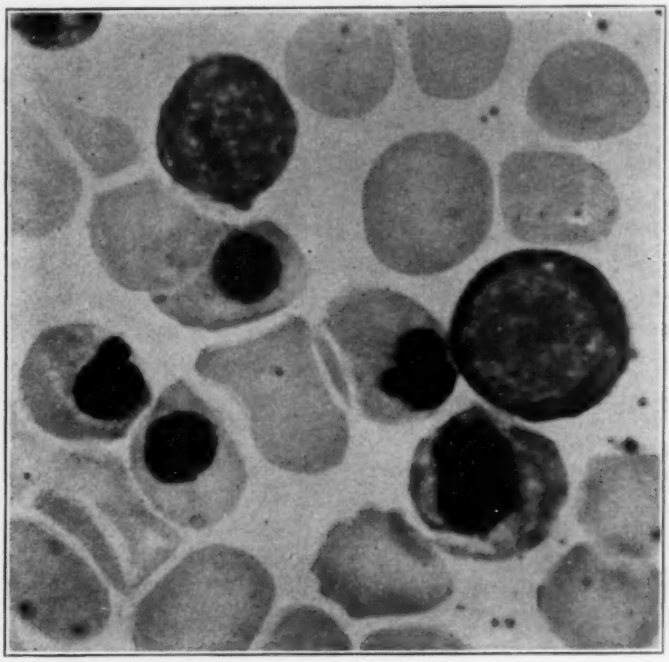

Fig. 11.—A smear of the cord blood of baby McK., showing several nucleated red cells and two megaloblasts. (Wright's stain; × 1,800.)

Other authors have previously incriminated the liver. Javert showed that his patients with hydrops had extremely low levels of plasma proteins, prothrombin and fibrinogen. The van den Berg reaction in erythroblastotic patients is biphasic or direct. Numerous necropsy reports indicate

16. Kato, K.: Monophyletic Scheme of Blood Cell Formation for Clinical and Laboratory Reference, J. Lab. & Clin. Med. **20**:1243, 1935. Israels, M. C. G.: The Pathological Significance of the Megaloblast, J. Path. & Bact. **49**:231, 1939. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 59. Dameshek and Valentine.[5] Jones.[6]

extensive hepatic damage [17] in cases of hydrops. In these there is usually extensive and often almost complete necrosis of the hepatic parenchyma, whereas in milder cases of icterus gravis there is less severe necrosis, and in the mildest ones there are only slight evidences of hepatic cellular damage. Varying degrees of extramedullary hemopoiesis are observed in the liver in all types. Several cases of portal cirrhosis in children who had recovered from icterus gravis neonatorum are reported in the literature.[18]

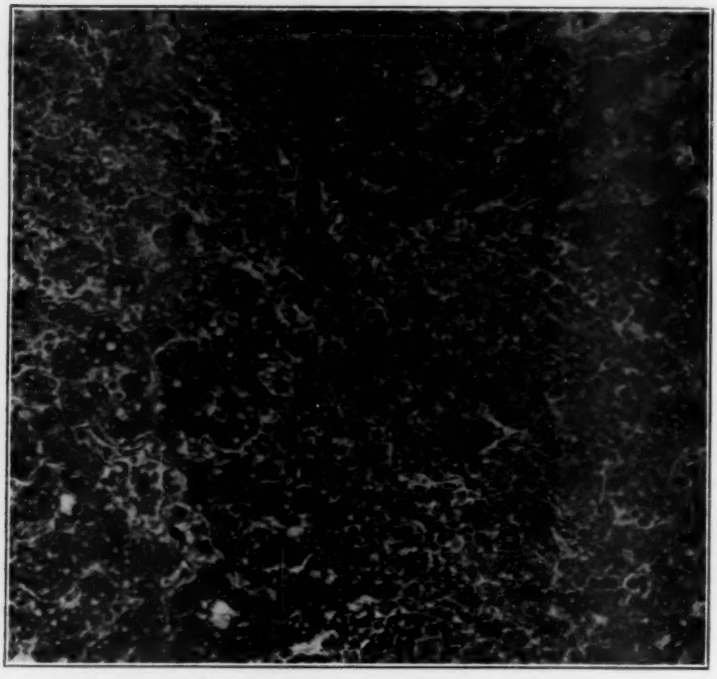

Fig. 12.—A section of the liver of baby TH., showing severe hemorrhagic necrosis, extramedullary hemopoiesis and hepatic cellular degeneration. (Hematoxylin and eosin; × 450.)

17. Polayes, S. H.: Pathology of Erythroblastosis Fetalis, read at a meeting of the New York Pathological Society, New York Academy of Medicine, Jan. 22, 1942. Parsons, L. G.; Hawksley, J. C., and Gittins, R.: The Hemolytic (Erythronoclastic) Anemias of the Newborn Period with Special Reference to Erythroblastosis of the Newborn, Arch. Dis. Childhood **8**:159, 1933. Diamond, Blackfan and Baty.[12] Hawksley and Lightwood.[13] Javert.[15]

18. Braid, F., and Ebbs, J. H.: Atrophic Cirrhosis of the Liver Following Icterus Gravis Neonatorum, Arch. Dis. Childhood **12**:389, 1937.

Darrow [4] suggested that the observed hepatic damage could be explained on the basis of a hypothetic antigen-antibody reaction, citing the work of Weil [19] and Dean and Webb,[20] who studied the changes in the liver in dogs during anaphylactic shock. Darrow expressed the opinion that the erythroblastemia might be at least partly attributable to increased hemopoietic activity in response to lower arterial oxygen tension due to hepatic damage.[21] Dean and Webb [22] showed that within two minutes after anaphylactic shock had been produced in the dog the number of nucleated erythrocytes in the blood underwent a marked increase, as much as forty times the normal number. In a case of anaphylaxis in man [23] Dean reported extensive hemorrhage and necrosis in the liver. More recently Hartley and Lushbaugh [24] have shown that focal necrosis of the liver can be produced in sensitized rabbits and guinea pigs by injecting sublethal doses of antigenic serum. While these facts have a suggestive bearing on the present problem, it is wise to be cautious in applying them to human pathology. It remains to be shown whether focal necrosis occurs in the livers of animals given hemolyzing antiserum. In a patient with an autohemolysinic anemia Farrar and associates [1c] observed severe hepatic damage, which improved when the spleen was removed and hemolysis presumably stopped.

Since the discovery of the role of the liver in the pathogenesis of pernicious anemia many observers have reported the presence of macrocytic anemia as an accompaniment of various types of hepatic disease.[25]

19. Weil, R.: Anaphylaxis in Dogs: A Study of the Liver in Shock and in Peptone Poisoning, J. Immunol. **2**:525, 1917.

20. Dean, H. R., and Webb, R. A.: The Morbid Anatomy and Histology of Anaphylaxis in the Dog, J. Path. & Bact. **27**:51, 1924.

21. Judd, E. S.; Snell, A. M., and Hoerner, M. T.: Transfusion for Jaundiced Patients, J. A. M. A. **105**:1653 (Nov. 23) 1935.

22. Dean, H. R., and Webb, R. A.: The Blood Changes in Anaphylactic Shock in the Dog, J. Path. & Bact. **27**:65, 1924.

23. Dean, H. R.: The Histology of a Case of Anaphylactic Shock Occurring in a Man, J. Path. & Bact. **25**:305, 1922.

24. Hartley, G., and Lushbaugh, C. C.: Experimental Allergic Focal Necrosis of the Liver, Am. J. Path. **18**:323, 1942.

25. Schulten, H., and Malamos, B.: Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, Klin. Wchnschr. **11**:1338, 1932. Fellinger, K., and Klima, R.: Untersuchungen über Anämien bei Leberzirrhosen, Wien. klin. Wchnschr. **46**:1191, 1933. Gamma, C.: Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, Klin. Wchnschr. **12**:348, 1933. Cheney, G.: The Morphology of the Erythrocytes in Cirrhosis and Other Disorders of the Liver, California & West. Med. **39**:90, 1933. van Duyn, J., Jr.: Macrocytic Anemia in Disease of the Liver, Arch. Int. Med. **52**:839 (Dec.) 1933. Wright, D. O.: Macrocytic Anemia and Hepatic Cirrhosis, Am. J. M. Sc. **189**:115, 1935. Rosenberg, D. H., and Walters, A.: Macrocytic Anemia in Liver Disease, Particularly Cirrhosis, ibid. **192**:86, 1936. Wintrobe, M. M.: Relation of Disease of the Liver to Anemia, Arch. Int. Med. **57**:289 (Feb.) 1936. Schalm, L.: The Average Red Blood Cell Diameter in Liver Disease and Jaundice, Acta med. Scandinav. **93**:513, 1938.

Macrocytosis has also been reported in animals with experimentally produced hepatic damage.[26] Briese [27] administered carbon tetrachloride vapor to pregnant rats during their gestation period and observed a slightly larger cell diameter and volume and a lower red cell count in the offspring, which she attributed to the impairment of the maternal supply of erythrocyte maturation factor.

Wintrobe and Shumacker [28] showed that the red cells in the maturing fetus exhibit changes similar to those of red cells in a person with pernicious anemia undergoing liver therapy, e. g., decreasing size and increasing number. This work was confirmed by Nishida.[29] From this Wintrobe and Shumacker postulated that as the fetal liver matured, more erythrocyte maturation factor was available for hemopoiesis. Since then various contradictory reports as to the effect of liver extract on the cells of developing embryos have been made, but two recent studies by Stasney and Burns [30] and Jones [31] indicate that the maturation of fetal red cells may be accelerated by the administration of both liver and gastric juice.

With this review of clinical and experimental facts it is perhaps permissible to formulate a tentative explanation for the observations reported in this paper. Bearing in mind that the final word has not yet been said on the subject of the Rh factor, one may assume that the fetal blood in erythroblastosis foetalis contains antigens, inherited from the father, which the mother lacks. One of these is Rh; another is hR, and there are probably others as yet undiscovered. Through a defect in the placenta fetal red cells enter the maternal circulation,[32] and antibodies

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26. Wintrobe, M. M., and Shumacker, H. B.: Morphologic Changes in the Blood Associated with Experimentally Produced Hepatic Damage, J. Clin. Investigation **15**:455, 1936. Rodriguez-Molina, R.: Experimental Liver Damage Associated with Hematological Changes in Hogs, Puerto Rico J. Pub. Health & Trop. Med. **15**:362, 1940. Higgins, G. M., and Stasney, J.: The Peripheral Blood in Experimental Cirrhosis of the Liver, Folia haemat. **54**:129, 1934.

27. Briese, E.: The Effect on the Blood Cells of the Fetal Rat Produced by the Inhalation of Carbon Tetrachloride by the Mother During Gestation, Am. J. M. Sc. **195**:787, 1938.

28. Wintrobe, M. M., and Shumacker, H. B.: Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, J. Clin. Investigation **14**:837, 1935.

29. Nishida, K.: Entwicklungsgeschichtliche Studie über die Blutbildung des japanischen Embryos: II. Messung des Erythrozytendurchmessers in der Leber des Embryos, Nagasaki Igakkwai Zassi **17**:929, 1937.

30. Stasney, J., and Burns, E. L.: Influence of Active and Inactive Antianemic Principles upon the Erythrocytes of the Immature Opossum, Am. J. M. Sc. **203**: 191, 1942.

31. Jones, O. P.: Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis: Quantitative Effects of Diet Containing Ventriculin, Arch. Int. Med. **68**:476 (Sept.) 1941.

32. Javert has recently demonstrated hematomas in the placentas of erythroblastotic infants (Further Studies on Erythroblastosis Neonatorum of Obstetric Significance, Am. J. Obst. & Gynec. **43**:921, 1942).

against them are produced. These antibodies are transmitted diaplacentally to the fetus, in which an antigen-antibody reaction takes place. Hemolysis occurs, accompanied or followed by damage to the liver and perhaps to other organs. During the phase of hemolysis the blood cells probably become smaller and spheroid in shape, but since this reaction occurs *in utero* it cannot be demonstrated clinically. Soon there is an admixture of larger new cells in the blood stream which arise in the marrow and the extramedullary hemopoietic centers. If the degree of hepatic damage is severe, adequate fetal supplies of erythrocyte maturation factor are not available and megaloblastic erythropoiesis takes place. The less mature the fetus the more marked this reaction is likely to be. Javert [15] has shown that babies with hydrops are usually premature, while the babies with icterus gravis are more likely to be full term. This may be the explanation for the generally larger cell diameters observed in some of our cases of hydrops (fig. 1). Babies with strong antigen-antibody reactions may have more severe hepatic damage and present the clinical picture of fetal hydrops; those with less severe reactions have icterus gravis, and those with the least severe reactions show only the effect of the blood destruction and their condition is called congenital anemia of the newborn.

The possible implications of this work for therapy are apparent, but too much should not be expected from liver therapy in patients with erythroblastosis. According to most observers, the macrocytic anemias of hepatic disease do not respond well to injection of liver extract, although Goldhamer and associates [33] have reported 2 cases of macrocytic anemia in cirrhosis of the liver in which the response was good. Their work suggested that acute hepatic damage may interfere with the proper utilization of liver extract, aside from its possible effect on the storage of the erythrocyte maturation factor. Bernheim-Karrer and Grob [34] fed large amounts of liver during the last ten weeks of pregnancy to a woman who had previously borne 2 erythroblastotic infants. The infant was born with a normal blood count and only mild icterus. Javert, on the other hand, has tried administering injections of liver extract to mothers ante partum, without affecting the outcome. Other authors have also tried liver therapy.[35] It must be remembered that the blood destruction going on simultaneously with impaired regeneration in erythroblastosis militates against successful liver therapy. However, it

33. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Rôle of the Liver in Hematopoiesis, Am. J. M. Sc. **188**:193, 1934.

34. Bernheim-Karrer, J., and Grob, M.: Zur Prophylaxe des Icterus Neonatorum Gravis, Ztschr. f. Kinderh. **50**:672, 1930.

35. Cooley, T. B.: Round Table Conference on Diseases of the Blood and Hematopoietic System, J. Pediat. **1**:635, 1932. Clifford, S. H., and Hartig, A. T.: Erythroblastosis of the Newborn, New England J. Med. **207**:105, 1932. Hampson, A. C.: Jaundice in the Newly Born, Practitioner **131**:59, 1933.

seems reasonable to suggest injections of liver extract as an adjuvant to transfusion therapy, particularly during the recovery phase in patients with this disease.

Finally, the question is raised whether hepatic damage may play a role in the production of other macrocytic hemolytic anemias in human beings or in animals.[36]

SUMMARY

Price-Jones curves were made on cord blood or peripheral blood in 12 cases of fetal hydrops and 12 cases of icterus gravis at the onset of illness. In 23 cases a characteristic biphasic curve, consisting of a normocytic and a macrocytic peak or two macrocytic peaks, was observed. In 1 case a monophasic microcytic curve was observed. A blood smear in this case revealed the presence of spherical microcytes, but three months later the smear was normal.

The morphologic changes in erythrocytes in erythroblastosis foetalis resemble, in some respects, those observed in experimental hemolytic anemias due to antigen-antibody reactions.

Examination of blood smears in 6 cases of severe erythroblastosis foetalis revealed varying numbers of megaloblasts. Postmortem examination in 4 cases revealed varying degrees of hepatic damage. The suggestion is made that the presence of megaloblasts and the macrocytosis, in part at least, may be the result of deficient erythrocyte maturation factor due to hepatic damage.

The blood destruction in this disease is believed to be best explained on the basis of an antigen-antibody reaction in the fetus, as suggested by other investigators. It is suggested that the hepatic damage may possibly be due to the same cause.

REPORT OF EIGHT CASES

CASE 1 (fig. 2).—Baby D., Jewish, was hospitalized from September 30 to Oct. 25, 1937.

Familial History.—The mother, aged 29, had had a thyroidectomy for exophthalmic goiter several years previously. In 1936 she had borne a normal infant, who was living and well. There was no history of jaundice in either side of the family.

Past History.—The patient had been born one week before the expected date and weighed 4,000 Gm.

Present Illness.—At birth the infant had been moderately icteric, and the jaundice persisted until admission. On the sixth day of life she was listless and feeble. The next day twitchings of the eyelids and the mouth were observed, and she was transferred to the pediatric ward.

36. Dyke, S. C., and Young, F.: Macrocytic Hemolytic Anaemia Associated with Increased Cell Fragility, Lancet **2**:817, 1938. Lambie, C. G.: Macrocytosis in Hereditary Hemolytic Anemia (Alcholuric Jaundice) with Report of a Case, M. J. Australia **2**:285, 1938. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in Series of Thirty-Five Cases, Ann. Int. Med. **12**:1782, 1939.

Physical Examination.—On admission the positive physical findings were poor activity and cry, moderate icterus and clonic twitches of the eyelids. The head and the chest both measured 34.5 cm. The eyes were somewhat slitlike, but there were no other signs suggestive of mongolism. The conjunctivas were pale and the scleras icteric. The heart and lungs were normal. The edge of the liver was palpable 1 cm. below the costal margin. The reflexes were hyperactive. The spleen was not palpable.

Laboratory Data.—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	Date	Hemoglobin, Gm./100 Cc.	Red Cells	White Cells	Nucleated Red Cells per 100 White Cells
	9/30/37	12.0	3,480,000	11,240	1
	10/3/37			26,000	3
	10/4/37	10.8	3,100,000	28,200	6
	10/13/37	12.6	4,580,000		0
	8/9/38	13.0	5,850,000		

	Date	Value
Icteric index	9/30/37	125
	10/4/37	150
	10/13/37	34
	10/21/37	9
Mean cell volume	10/3/37	109.8 cu. mm.
Reticulocytes	10/15/37	7%

		Patient		Control	
	Date	Beginning Hemolysis	Complete Hemolysis	Beginning Hemolysis	Complete Hemolysis
Red cell fragility in hypotonic solution of sodium chloride	10/5/37	0.50	0.36	0.42	0.32
	10/6/37	0.60	0.34	0.42	0.26*
	10/13/37	0.44	0.34	0.44	0.26*
	8/11/38	0.46	0.36	0.46	0.36
Culture	10/1/37	No growth			
Kline reaction	10/1/37	Negative			

* These control values show an unusually low level of complete hemolysis and may represent errors in technic. It is felt that they could not rightfully be omitted, however, and I do not believe they impair the significance of the values obtained with the patient's blood.

Course of Illness.—On the day of admission and on the following day the patient was transfused with blood of her father. After the second transfusion, the temperature rose, she became deeply jaundiced and the liver and the spleen enlarged so that they were palpable 2 cm. and 5 cm. respectively below the costal margin. This condition persisted for several days, during which time several additional transfusions were given with a different donor. After this the icterus disappeared and the patient made an uneventful recovery and was discharged on October 25. In August of the following year (Aug. 11, 1938) she was readmitted with convulsive seizures and failure to develop properly. On this admission an air encephalogram showed cerebral cortical atrophy. The blood

count and the red cell fragility on this admission were normal. Since her discharge on that admission she has not been seen again in the New York Hospital Children's Clinic.

CASE 2 (fig. 2).—Baby TH., Negro, was hospitalized Jan. 26 and 27, 1942.

Familial History.—The father, aged 33, was living and well, and the Wassermann reaction of his blood was negative. The mother, aged 33, had been discovered to have a positive Wassermann reaction in the seventh month of pregnancy. Since then she had been treated with sixteen injections of arsphenamine and nine injections of a bismuth compound. Her blood did not contain Rh antigen.

Past History.—The infant had been delivered normally at full term. The weight at birth was 2,450 Gm. The vernix caseosa was icteric. The baby was slow to breathe and was transferred directly to the pediatric ward.

Physical Examination.—The baby's color, cry and activity were poor. Scattered petechiae were present on face, scalp and neck. The upper gum was cleft. The lungs were clear. The heart showed a soft systolic murmur. The liver and spleen were both palpable 1 cm. below the costal margin.

Laboratory Data.—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	
Hemoglobin, Gm./100 cc.	20.0
Red cells	6,300,000
White cells	14,700
Nucleated red cells/100 white cells	500
Wassermann reaction, 1:4 dilution	++++
Prothrombin	< 4%
Culture	No growth

Course of Illness.—The night of admission the chest filled with rales, and the infant was put in an oxygen tent. The next morning he had several generalized convulsions, became cyanotic and died. A roentgenogram of the long bones failed to reveal any evidence of syphilis of the bone.

Autopsy.—The main findings at autopsy were in the liver. This organ was grossly enlarged and weighed 125 Gm. The surface was dark purple red. There was an increase of grayness in the cut section, and lobular markings were not visible. Microscopically, the hepatic cells had lost their architecture, stained faintly and often showed disintegrated nuclei. There were many red cells present in these areas. The viable liver cells present showed extreme vacuolization. There were small islands of erythropoiesis (fig. 12). The anatomic diagnosis included erythroblastosis foetalis and prematurity. There was no evidence of congenital syphilis.

CASE 3 (fig. 3).—Baby B., Irish, was hospitalized from February 10 to April 14, 1942.

Familial History.—The mother, aged 37, was living and well. Her blood did not contain Rh antigen and she had anti-Rh antibodies. The father was living and well, and his blood contained Rh antigen. Four siblings were living and well. There was no history of icterus.

Past History.—The infant had been delivered normally at full term, after a normal pregnancy. The weight at birth was 3,650 Gm.

Present Illness.—On arrival in the nursery the infant was noted to be icteric and became more so during the next seven hours. A smear of blood showed numbers of erythroblasts, and the infant was transferred to the pediatric service.

Physical Examination.—Marked icterus of skin, cord and scleras was present. The skin appeared generally puffy but did not pit on pressure. It was covered with scattered fine petechiae. The liver was palpable 3 cm. below the costal margin, and the spleen, 2 cm. below the costal margin.

Laboratory Data.—The results of laboratory examination have been tabulated as follows:

Urine on admission	
Color	Reddish brown
Albumin	++
Red cells per high power field	10-65
White cells	Occasional
Granular cells	Occasional
Blood count	
Hemoglobin, Gm./100 cc.	12.0
Red cells	4,000,000
White cells	35,000
Nucleated red cells/100 white cells	54
Icteric index	107
Prothrombin	20%
Rh antigen	Present
Kline reaction	Negative

Course of Illness.—For the first two days he was given daily intramuscular injections of menadione (vitamin K) in oil and blood transfusions. The blood count did not rise; the number of nucleated red cells increased slightly, and the icterus deepened. Two more transfusions from another donor were given, and the number of red cells and the hemoglobin level increased and stayed up, and the nucleated red cells diminished in number and were not seen after February 15. Meanwhile, however, the jaundice deepened, the urine began to give a positive reaction for bile and the stools became light in color. On February 19, the icteric index was 250 and the van den Bergh reaction was positive (immediate direct). After two weeks, the icterus gradually diminished, the urine became bile free and the stools became normally pigmented. Recovery was retarded by an infectious diarrhea which was treated with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). Just before discharge the icteric index was 12.5; prothrombin was 57 per cent, and bromsulphalein dye was absent from the blood thirty minutes after injection. The hemoglobin level was 13.5 Gm. per hundred cubic centimeters, and the red cell count was 3,580,000 on discharge on April 14.

Case 4 (fig. 4).—Baby FL., Irish, was hospitalized from October 4 to Nov. 16, 1941.

Familial History.—The mother, aged 31, was living and well, and her blood did not contain Rh antigen. The father's blood contained this antigen. The first sibling was living and well. Three siblings had died of erythroblastosis. A fifth sibling, living and well, had been icteric at birth.

Past History.—Pregnancy had been uneventful, lasting forty-three weeks. The mother had received menadione for two weeks before delivery. The weight at birth was 4,400 Gm.

Present Illness.—The infant breathed poorly after birth and received 1 cc. of menadione in oil [37] intramuscularly in the nursery. A smear of blood at birth showed erythroblastosis, and the baby was transferred to the pediatric service.

37. The menadione in oil used in these cases contained 1 Gm. of menadione in each cubic centimeter.

Physical Examination.—The temperature was 37 C. (98.6 F.), and the pulse rate was 120 per minute. No icterus or edema was apparent seven hours after birth. The cord was moderately icteric. Positive physical findings were a liver palpable 3 cm. and a spleen palpable 1 cm. below the costal margin. The infant became icteric during the first few days of life.

Laboratory Data.—A blood count revealed 16.0 Gm. of hemoglobin per hundred cubic centimeters, 4,200,000 red cells, 11,800 white cells and 214 nucleated red cells per hundred white cells. The blood contained Rh antigen and gave a negative Kline reaction.

Course of Illness.—With repeated transfusions the infant did well except for occasional vomiting. The number of red cells and the hemoglobin level tended to fall at first but were kept up with repeated transfusions. Nucleated red cells disappeared after October 10. The infant was discharged on November 16 and was doing well when last seen.

Case 5 (fig. 5).—Baby I., American, was hospitalized from October 18 to Nov. 16, 1941.

Familial History.—The mother, aged 29, was living and well and did not have Rh antigen in her blood. The father, aged 30, was living and well and had Rh antigen. One sibling, aged 17 months, was living and well.

Past History.—Pregnancy had been uneventful. The infant's weight at birth was 3,040 Gm.

Present Illness.—The vernix caseosa and the amniotic fluid were noted to be yellow at birth. The infant received 1 cc. of menadione in oil intramuscularly on admission to the nursery. Icterus was noted in the nursery, examination of a smear of blood and a blood count revealed the condition, and she was transferred to the pediatric service.

Physical Examination.—Positive physical findings included deep icterus of skin, scleras and umbilical cord. The liver was palpable 2 cm. and the spleen 1 cm. below the costal margin.

Laboratory Data.—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	
Hemoglobin, Gm./100 cc.	12.0
Red cells	3,000,000
White cells	28,000
Nucleated red cells/100 white cells	30
Prothrombin	7 %
Icteric index (10-20-41)	68
Rh antigen	Present
Kline reaction	Negative

Course of Illness.—The icterus was maximal on the second day and then faded. Transfusions were given on the first four days. Nucleated red cells were not seen after October 21, and the number of red cells and the hemoglobin content rose to normal levels by the time of discharge on November 16.

Case 6 (fig. 6).—Baby FT., Jewish, was hospitalized from January 30 to Feb. 18, 1942.

Familial History.—The mother, aged 30, was living and well. Her blood contained Rh antigen but not hR antigen. In 1939 a full term infant had been delivered by cesarian section for fetal distress; the infant had died at the age of 1 day. Autopsy,

performed in another hospital, was said to reveal atelectasis. There was no mention of erythroblastosis.

Past History.—The infant was delivered by cesarian section three weeks after the expected date of confinement. The baby breathed and cried poorly and was transferred to the pediatric service immediately after birth.

Physical Examination.—The infant was small, weighing 2,550 Gm., with a good cry, no cyanosis and normal respirations. The skin had an icteric tint, and there was slight edema of the eyelids. The edge of the liver was palpable 0.5 cm. below the costal margin; the spleen was not palpable.

Laboratory Data.—A blood count revealed 18.0 Gm. of hemoglobin per hundred cubic centimeters, 6,400,000 red cells, 16,000 white cells and 32 nucleated white cells. The next day the hemoglobin content remained the same, but the red cell count had fallen to 4,600,000, the white cell count had increased to 20,000 and there were 60 nucleated red cells per hundred white cells. The blood contained hR antigen.

Course of Illness.—After a single transfusion of blood the nucleated red cells fell to 6 per hundred white cells and then disappeared entirely, and the smear, which had showed marked anisocytosis and polychromasia, became normal. The icterus disappeared after the third day, and the baby was discharged from the nursery on February 18.

Case 7 (fig. 7).—Baby WE., American, was hospitalized from April 23 to May 22, 1942 (he was still in the hospital when this report was prepared).

Famial History.—The mother, aged 34, was living and well and did not have Rh antigen in her blood. The father, aged 36, was living and well and had Rh antigen. The mother had had a miscarriage at three months in 1932. One sibling, who was living and well, had been icteric for several days after birth in 1933. One sibling had died of erythroblastosis foetalis in 1940.

Past History.—Pregnancy and delivery had been normal. The mother had received menadione for several weeks prior to delivery. The infant's weight at birth was 3,340 Gm.

Present Illness.—Because of the family history the infant was transferred directly from the delivery room to the pediatric ward.

Physical Examination.—Positive findings on admission included a soft blowing systolic murmur at the apex of the heart and a liver palpable 2 cm. and a spleen palpable 1 cm. below the costal margin. There was no visible icterus on admission nor any petechiae or ecchymoses. Neurologic findings were within physiologic limits.

Laboratory Data.—The results of laboratory examination of the blood have been tabulated as follows:

Blood count	4/23/42	5/19/42
Hemoglobin, Gm./100 cc.	17.5	10.8
Red cells	5,000,000	2,660,000
White cells	22,080	
Nucleated red cells/100 white cells	15	
Rh antigen	Present	
Kline reaction	Negative	
Serum protein, mg./100 cc. (4/25/42)	5.2	
Icteric index (5/4/42)	150	

Course of Illness.—Shortly after admission jaundice appeared and steadily increased during the first ten days. On the third day the infant was listless and

spastic with opisthotonos, carpopedal spasm and muscular twitchings. A lumbar puncture revealed xanthochromic spinal fluid loaded with red cells. At the same time the serum calcium level was 8.2 mg. per hundred cubic centimeters. Both menadione and calcium chloride were given intramuscularly, and the neurologic signs diminished in severity by the end of a week, but opisthotonos and hypertonicity were still present. On the seventh day of life, the stools became clay colored and the urine gave a positive reaction for bile. This persisted for several days, after which the icterus gradually diminished in intensity. During the first week of his illness the infant received daily blood transfusions. After this they were given only when the fall in the blood count indicated that hemolysis was proceeding. By the third day nucleated red cells had disappeared from the peripheral blood. The recovery was uneventful until the twentieth day, when diarrhea developed with an accompanying fall in the red cell count to 2,660,000. At present he has recovered from this and is only faintly icteric.

CASE 8 (fig. 8).—Baby C., American, was hospitalized from May 3 to 5, 1942.

Familial History.—Both the mother and the father were living and well. Rh antigen was present in the father's blood but not in the mother's. The mother's first pregnancy, with a different husband in 1938, had resulted in an inevitable abortion at five months. Her second pregnancy, with the present husband, had been normal; the child was living and well. Her present pregnancy had been uneventful.

Past History.—Delivery had been normal; the infant's weight at birth was 3,400 Gm.

Present Illness.—A few hours after birth the infant was noted to be icteric and was transferred to the pediatric ward.

Physical Examination.—On admission the infant was deeply jaundiced, had a good cry and activity, but showed clonic twitchings of the lower extremities. The reflexes were hyperactive. The spleen was palpable 2 cm. below the costal margin. The liver was not felt. The results of the remainder of the examination were irrelevant.

Laboratory Data.—The results of the laboratory examination of the blood have been tabulated as follows:

Blood count	5/4/42	5/5/42
Hemoglobin, Gm./100 cc.	14.5	11.0
Red cells	2,700,000	2,350,000
White cells	15,500	
Nucleated red cells/100 white cells	7	18
Rh antigen	Present	
Kline reaction	Negative	
Serum protein, mg./100 cc.	5.0	
Prothrombin	< 2%	

Course of Illness.—On admission a transfusion of citrated bank blood was given, along with intramuscular injections of liver extract and menadione in oil (2 cc.). The blood count rose temporarily after the transfusion but then fell, and the jaundice deepened. On the morning of the third day the infant suddenly became drowsy, spastic and cyanotic and seemed to be on the verge of respiratory failure. Another transfusion and an infusion of solution of sodium chloride were gvien, in addition to stimulants and oxygen, but the patient's condition grew worse and he died late that afternoon, after vomiting some blood-tinged matter.

Autopsy.—The significant observations post mortem included generalized, moderate icterus and kernicterus; hepatomegaly (weight of liver 200 Gm.); plenomegaly (weight of spleen 36 Gm.); partial atelectasis; hemorrhages in the gastrointestinal tract, lungs, kidneys and adrenals, and pseudomembranous esophagitis.

Microscopic examination of the liver revealed numerous areas of erythrogenic and myelogenic hemopoiesis. The parenchymal cells were moderately well stained with fair preservation of the architecture and occasional deposits of brown pigment. Similar pigment was also observed in some of the Kupffer cells.

The final diagnosis was erythroblastosis foetalis.

SPONTANEOUS MEDIASTINAL EMPHYSEMA

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Mediastinal emphysema following stab wounds or other trauma of the chest has long been recognized. It has also been described as occurring secondary to violent coughing, bronchial asthma, artificial pneumothorax, pneumonia, difficult labor, straining at stool and other forms of extreme effort. McGuire and Bean [1] point out that Laennec [2] described grating sounds and bubbling rales during respiration as diagnostic of subpleural and interlobar emphysema. Skoda [3] subsequently confirmed these signs, and von Rokitansky [4] described the pathologic aspects of the condition. Müller [5] noted the presence of bubbling crepitations that occurred with the heart beat and the occasional disappearance of cardiac dulness. He observed that the presence of subcutaneous emphysema aided in making the diagnosis of mediastinal emphysema.

Rees and Hughes [6] in a report on wounds of the chest encountered during World War I noted loud "tapping" sounds over the cardiac area in 9 cases of wounds of the left side of the chest. They observed that the sound continued even when the breath was held, although it was louder during inspiration; the sound was synchronous with the heart beat. In some cases, the examiner could hear the noise several paces from the chest and patients at times were also aware of the sounds. Smith [7] subsequently applied the term pericardial knock to this sound, comparing it to a "noise which may be heard in the ear-piece of a tele-

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1. McGuire, J., and Bean, W. B.: Spontaneous Interstitial Emphysema of the Lungs, Am. J. M. Sc. **197**:502-509 (April) 1939.

2. Laennec, R.: Traité de l'auscultation médiate, ed. 3, Paris, J. S. Chaudé, 1831, vol. 1, p. 329; cited by McGuire and Bean.[1]

3. Skoda, J.: Abhandlung über Percussion und Auscultation, ed. 4, Vienna, L. W. Seidel, 1850, p. 276; cited by McGuire and Bean.[1]

4. von Rokitansky, K.: Lehrbuch der pathologischen Anatomie, ed. 3, Vienna, Wilhelm Brausmüller, 1856, vol. 2, p. 12; cited by McGuire and Bean.[1]

5. Müller, F.: Ueber Emphysem des Mediastinum, Berl. klin. Wchnschr. **25**: 205-208, 1888; cited by McGuire and Bean.[1]

6. Rees, W. A., and Hughes, G. S.: Wounds of the Chest as Seen at an Advanced Operating Center, Lancet **1**:55-59 (Jan. 12) 1918.

7. Smith, S. M. S.: Pericardial Knock, Brit. M. J. **1**:78 (Jan. 19) 1918.

phone when the lever is moved up and down." Lister's [8] case is the first one to be reported in which the sounds appeared spontaneously while the patient was at rest. Wolferth and Wood [9] observed a young man who had a spontaneous pneumothorax and who apparently had had a "pericardial knock." In this instance the patient stated that a wrestling match had preceded the onset of precordial pain. Fisher [10] and Biering [11] have described what they term spontaneous interstitial and mediastinal emphysema in a newborn infant, but this has always been secondary to congenital atelectasis.

Hamman [12] in 1934 described 3 spontaneous occurrences of this condition under the heading of interstitial emphysema and discussed the differential diagnosis from coronary closure. In 1937 Hamman [13] reported 4 additional spontaneous occurrences of the syndrome. In this paper he included 2 of his previously reported cases, omitting the one in which symptoms occurred after an operation on a paranasal sinus. Hamman [14] added another case to his series in 1939. McGuire and Bean [1] gave a comprehensive review of the 8 cases of spontaneous mediastinal emphysema that had been reported previously and added 2 of their own. They noted that in 1 of their cases the emphysema had its onset fifteen minutes after a difficult labor and therefore could not be classified as occurring spontaneously. In the other case that they reported the patient was a 17 year old girl, and the onset occurred when she was dribbling a basketball in a gymnasium. Consideration of this case as one of spontaneous mediastinal emphysema might be questioned inasmuch as it occurred during exertion. McGuire and Bean were the first to suggest that this entity be designated "Hamman's disease."

Morey and Sosman [15] in 1939 added another case to this small series. By roentgen study they were able to demonstrate the presence of a small

8. Lister, W. A.: A Case of Pericardial Knock Associated with Spontaneous Pneumothorax, Lancet **1**:1225-1226 (June 16) 1928.

9. Wolferth, C. C., and Wood, F. C.: Angina Pectoris, M. Clin. North America **13**:947-967 (Jan.) 1930.

10. Fisher, J. H.: Spontaneous Pulmonic Interstitial and Mediastinal Ephysema in an Infant, Canad. M. A. J. **44**:27-29 (Jan.) 1941.

11. Biering, A.: Pneumothorax in Newborn: Case of Pneumothorax with Congenital Atelectasis and Mediastinal Emphysema, and Some Remarks on Pathogenesis, with Special Reference to Importance of Congenital Atelectasis, Acta pædiat. **28**:367-384, 1941.

12. Hamman, L.: Remarks on the Diagnosis of Coronary Occlusion, Ann. Int. Med. **8**:417-431 (Oct.) 1934.

13. Hamman, L.: Spontaneous Interstitial Emphysema of the Lungs, Tr. A. Am. Physicians **52**:311-319, 1937.

14. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **64**:1-21 (Jan.) 1939.

15. Morey, J. B., and Sosman, M. C.: Spontaneous Mediastinal Emphysema, Radiology **32**:19-22 (Jan.) 1939.

pneumothorax. In 1941, 1 case of spontaneous mediastinal emphysema was reported by Matthews,[16] Pinckney [17] reported 2 cases and Caldwell [18] and Styron [19] reported 1 case each. If one omits the case reported by Wolferth and Wood [9] and the 2 cases reported by McGuire and Bean [1] because of the relation to effort, there are on record only 13 instances of this syndrome occurring spontaneously. It is of some significance that 5 of them were reported in the past year. Because of the ease with which the diagnosis is made and because of the importance of differentiating spontaneous mediastinal emphysema from various vascular accidents, it is deemed advisable to call attention again to this interesting syndrome and to add another case to the small group that has been reported.

REPORT OF A CASE

S. T., a 22 year old automobile mechanic, was admitted to Bellevue Hospital, Feb. 21, 1941, complaining of severe pain of one hour's duration in the chest on the left side. At the time the pain appeared he was sitting quietly in a chair reading a newspaper, and he stated that he had not done any strenuous work during that day. The pain was sharp and knifelike with a maximum intensity over the lower anterior portion of the chest on the left side from where it radiated straight through to the back. The pain was made worse by inspiration, and the patient had become somewhat short of breath. He was brought to the hospital by car, and when seen in the admitting office he stated that he heard noises in his chest which "sounded as if gears were grinding together." His familial history and his past history, including history of previous respiratory and cardiac disorders, were entirely irrelevant.

On admission his temperature was 99.4 F., respiration 18 per minute, pulse rate 90 per minute and blood pressure 130 systolic and 82 diastolic. He was well developed and well nourished and was not in any acute distress unless asked to inspire deeply. There was no dyspnea, orthopnea or cyanosis. The skin was warm and of good turgor. There were no abnormalities of the head, eyes, ears, nose or throat. The trachea was in the midline. No emphysema was noted in the tissues of the neck, but there was a definite area of subcutaneous emphysema over the lower portion of the anterior wall of the chest on the left side. The expansion of the thorax was good and equal. On placing the hand over the anterior aspect of the lower ribs on the left side during deep inspiration it felt as if two surfaces were being rubbed together and then pulled apart. The right hemithorax was clear to percussion and auscultation. On the left side the chest was resonant throughout, but the percussion note over the precordium seemed somewhat more resonant than usual. Anteriorly from the left costal margin to the third rib "boiler-like" sounds of loud intensity were heard; extending into

16. Matthews, E.: Spontaneous Mediastinal Emphysema, New Orleans M. & S. J. **93**:523-524 (April) 1941.

17. Pinckney, M. M.: Mediastinal Emphysema and Idiopathic Spontaneous Pneumothorax, Virginia M. Monthly **68**:315-319 (June) 1941.

18. Caldwell, H. W.: Spontaneous Mediastinal Emphysema, J. A. M. A. **116**:301-302 (Jan. 25) 1941.

19. Styron, C. W.: Spontaneous Mediastinal Emphysema, New England J. Med. **225**:908-909 (Dec. 4) 1941.

the axilla finer crackling sounds were audible. These "boiler-like" sounds might be compared to the noise that one hears on crumpling a handful of cellophane close to the ear and could be heard distinctly several feet from the patient's chest. The rest of the chest was clear. The heart was not enlarged, and it was not displaced either to the right or to the left. There was a normal sinus rhythm, and no murmurs were heard. At the time of this examination there was no correlation noted between the heart beat and the sounds in the chest. The remaining results of physical examination were entirely irrelevant.

An hour after admission, examination of the chest showed a marked decrease in the intensity of the "boiler-like" sounds but many coarse crackling noises were still heard over the same distribution and these seemed to be associated with the heart beat. Two hours after admission, the "boiler-like" sounds had disappeared completely and only a few crackles remained. By the following morning, eighteen hours after admission, all that could be heard were a few crackling sounds over the precordium appearing only during diastole and heard best with the patient lying on his left side. The patient felt fine and because he had not had any pain or discomfort since the previous evening insisted on going home.

A roentgenogram of the chest taken at the time of admission showed a small pneumothorax at the apex of the left lung. Other roentgenograms were taken in an effort to discover air in the mediastinum, but none could be made out. Because of the patient's short stay in the hospital, the laboratory examination was limited. His hemoglobin concentration was 90 per cent (Sahli), and the white cell count was 19,500, with 93 per cent polymorphonuclears and 7 per cent lymphocytes.

MECHANISM

Macklin [20] has investigated extensively the mechanism of spontaneous mediastinal emphysema. From experimental work on cats he has been able to demonstrate that with increased intrapulmonary pressure there is a distention of alveoli. With this distention of alveoli there occur many small ruptures in their floors, which overlie the small branches of the pulmonary blood vessels. As the pressure continues, air is forced onward through artificial tunnels in the vascular sheaths toward the root of the lung and may break through into the mediastinum, distending the tissues with large blebs. From this location the air may be forced upward into the root of the neck, the face, the axilla or the wall of the chest, or it may go forward between the parietal pleura and the pericardium. At times the air in the perivascular sheaths may extend into adjoining connective tissue and dissect a path toward the pleura, where a bleb may form under the pleura; this bleb can rupture and produce a pneumothorax. Hamman [14] stated that in man the alveoli may rupture, even though they show no gross evidence of disease. In view of this observation of Hamman, it may be assumed that it is possible for the alveoli to rupture in the absence of recognizable increased intrapulmonary pressure.

20. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**:913-926 (Nov.) 1939.

CLINICAL FEATURES

The distinctive sign of mediastinal emphysema is the crunching sound that is heard over the heart with each contraction. This noise has been explained as being produced by the compression of the air-filled mediastinal tissues which lie between the heart and the anterior wall of the chest. As has been stated, one can almost duplicate this sound by crumpling a handful of cellophane close to the ear. To one who is not aware of the possibility of this condition, the nature of the onset may cause him to think of coronary occlusion, pericarditis, ruptured or dissecting aneurysm or pulmonary embolus. Only by a knowledge of the clinical picture of spontaneous mediastinal emphysema will the patient be spared an unnecessarily prolonged convalescent period and a grave prognosis. The onset is sudden and terrifying to the patient. The pain may last a few hours or several days.

The reports of Hamman [21] have done much to bring this syndrome to the attention of members of the medical profession. The large number of cases of spontaneous mediastinal emphysema encountered by him and the careful reporting of his observations have constituted a noteworthy contribution. The following summary of important symptoms is taken from his most recent paper [14] on the subject:

1. Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

2. When the air reaches the mediastinum, distending the mediastinal tissues, the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum; sometimes it radiates to the back . . . [or] neck . . . [or] shoulders, rarely to the arms. . . .

3. There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leucocyte count are very little if any altered. [Other authors have reported an increased leukocyte count, such as occurred in my patient.]

4. In many instances a peculiar and distinctive sound is heard over the heart synchronous with its contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

5. The area of cardiac dulness may be diminished or completely obliterated, the dulness being replaced by a hyperresonant percussion note.

6. Pneumothorax often occurs. The pneumothorax is usually small and may [be detected only by roentgen examination]. . . .

7. The roentgenogram is a valuable aid in establishing the diagnosis [particularly in the absence of characteristic sounds over the heart. The detection by a roentgenogram] of air in the mediastinum may be decisive. . . .

8. When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

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21. Hamman (footnotes 12, 13 and 14).

SUMMARY

In this report I have added another instance of spontaneous mediastinal emphysema to the 13 [22] previously reported cases. Half of these cases have been observed by Hamman, and his description of this syndrome is classic. He has emphasized the sudden onset of spontaneous mediastinal emphysema and the significance of the crunching sound heard over the left side of the chest. The experimental work of Macklin has been an outstanding contribution toward the understanding of the mechanism and the pathology of this condition. It is important to differentiate spontaneous mediastinal emphysema particularly from coronary disease, but the picture may also be confused with that of pericarditis, ruptured or dissecting aneurysm and pulmonary embolus. The reporting of 5 cases of spontaneous mediastinal emphysema in the past year indicates that physicians are becoming aware of this picture and are prepared to recognize it. The diagnosis of spontaneous mediastinal emphysema is particularly important in preventing an unnecessarily prolonged convalescence and in saving a patient from unneeded precautions. Undoubtedly, as physicians become more cognizant of this syndrome the diagnosis will be made more frequently.

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22. Since this paper was written, reports of 8 additional cases of spontaneous mediastinal emphysema have appeared, making a total of 22, including the case reported here. These additional reports are as follows: Griffin, R. J.: A Diagnostic Sign of Interstitial Emphysema of the Mediastinum, Ann. Int. Med. **17**:295-297 (Aug.) 1942; Spontaneous Pneumothorax, Kentucky M. J. **39**:284-288 (Aug.) 1941. Wolfe, B. P.: Spontaneous Interstitial Emphysema of the Lungs, Ann. Int. Med. **13**:1250-1252 (Jan.) 1940. Murphy, J. P., and Zeis, L. B.: Spontaneous Interstitial Mediastinal Emphysema, J. Missouri M. A. **39**:5-7 (Jan.) 1942. Miller, J.: Spontaneous Interstitial Emphysema of the Lungs, Ohio State M. J. **37**:1056-1059 (Nov.) 1941.

Progress in Internal Medicine

REVIEW OF THE LITERATURE ON THE PITUITARY GLAND (1940 AND 1941)

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In recent years extensive experimental studies have been carried out in an attempt to delimit the functions of the pituitary body. A bewildering array of data has been accumulated; this tiny gland has been reported to be intimately related to many of the phases of body metabolism and to nearly every other endocrine gland in the body. An attempt to review fully each of the many phases of investigation which have been carried out would result only in confusion, both for the reader and for the reviewers. Consequently, we shall mention only the recent work on the more clearly established functions of the pituitary gland which may be of clinical significance.

The large number of separate hormones postulated as being elaborated by the pituitary, particularly its anterior lobe, has for some time aroused skepticism among the investigators in this field. Indeed, it does seem almost incredible that an organ the size of the pituitary gland, which has in its anterior lobe only two and in its posterior lobe only one type of acknowledged secretory cell, should elaborate so many different substances. Some investigators, therefore, have suggested that several or even all of the presumably individual hormones might represent cleavage products of larger molecular compounds, that is, artefacts produced by the physical and chemical procedures employed in their isolation. Abel and associates [1] first made this suggestion in connection with the secretion of the posterior lobe. Riddle [2]

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1. Abel, J. J.; Rouiller, C. A., and Geiling, E. M. K.: Further Investigations on the Oxytocic-Pressor-Diuretic Principle of the Infundibular Portion of the Pituitary Gland: II. A Preliminary Therapeutic Study of the Active Principle of the Infundibular Portion of the Pituitary Gland in Four Cases of Diabetes Insipidus, J. Pharmacol. & Exper. Therap. **22**:289-328 (Nov.) 1923.

2. Riddle, cited by Heller.[4]

and Collip and co-workers [3] have claimed that this concept also applies to the secretion of the anterior lobe. However, since it has been possible more recently to separate not only the pressor and the oxytocic principle from extracts of the posterior lobe but certain individual factors from extracts of the anterior lobe by mild, nonchemical procedures, such as fractional adsorption and electrophoresis, doubt has been cast on the claim that these individual principles represent artificial cleavage products. Heller [4] has suggested that the pituitary principles may not be secreted singly but in groups. Clinical evidence likewise suggests this mode of secretion.[5] Tumors of any secreting cells of the anterior lobe are associated with symptoms which suggest an abnormal secretion of constant groups of factors.

In spite of all this evidence, the question of whether the various types of pituitary cells are capable of secreting each factor singly or their secretion consists of large molecules having multiple activity, the action of which depends on the response of the effector tissue, still awaits final solution. Isolation of the individual factors in pure chemical form plus more accurate demonstration that they exist in the pituitary gland and in the body fluids in significantly different amounts will soon be accomplished, it is hoped.

THE ANTERIOR LOBE OF THE PITUITARY GLAND

Sevringhaus [6] has stated:

> Among the disturbances of the several functions of the anterior lobe of the pituitary, only two are susceptible to treatment with any assurance of success at present. These are dysfunctions in the supply of the growth-promoting and gonadotropic factors.

Many physicians doubt whether even these two disturbances can be treated with any assurance of success. However, since these two factors have received most attention from investigators in the field of pituitary function, we shall consider them first.

THE GROWTH HORMONE OF THE ANTERIOR LOBE

Experimental Aspects.—Just as normal growth is dependent on a multiplicity of extrinsic factors, so also is it influenced by many intrinsic factors; more than one of the glands of internal secretion

3. Collip, J. B., and others: Symposium: The Anterior Pituitary Gland and Its Neuro-Endocrine Relationships, Tr. Am. Neurol. A. **61**:7-17, 1935.

4. Heller, H.: Multiplicity of Pituitary Hormones, Nature, London **147**:178 (Feb. 8) 1941.

5. Cameron, cited by Heller.[4]

6. Sevringhaus, E. L.: Dysfunctions of the Anterior Lobe of the Pituitary and Their Treatment, J. A. M. A. **116**:221-225 (Jan. 18) 1941.

have been shown to have definite relations to growth. Consequently, the claim that the pituitary gland elaborates a hormone essential for growth has only gradually gained validation. There is still some question as to whether the pituitary gland regulates growth through the direct action of a "growth hormone" or through an effect on one or more of the other endocrine glands, the target organs, known to be influenced by the hypophysis. The bulk of the evidence obtained to date seems to indicate that growth-stimulating extracts of the anterior lobe of the pituitary gland do not obtain their result by virtue of their content of the four well known principles affecting target organs (thyrotropic, lactogenic, adrenotropic and gonadotropic principles [6]). Reinhardt and his co-workers [7] have reported that the thymus likewise is not a target organ through which the effect of the growth principle is mediated. Evans [8] has made the definite statement that the growth factor is "clearly separate from the target organ hormones." He doubts, however, that "an equally decisive answer" can be given as to whether

> . . . the promotion of growth by anterior pituitary extracts is due to one or more of the incompletely separated metabolic "hormones" of the anterior lobe, i. e., the ketogenic, glycotropic, glycostatic, contrainsular, diabetogenic, pancreatropic, nitrogen-retaining and other factors.

The exact mode of action of the growth principle is still unknown. Greene and Johnston [9] reported that balance studies of nitrogen, sulfur, calcium and phosphorus made on 3 typical primary pituitary dwarfs and on 3 nonpituitary dwarfs both before and after the administration of growth-promoting extracts of the anterior lobe showed that the immediate effect was to decrease storage of these elements and the later effect was to increase their storage. Mirsky [10] suggested that extracts of the anterior lobe had two effects on protein metabolism, a direct one on protein catabolism in the muscles and an indirect one, mediated through the pancreas, stimulating protein anabolism. Thus, the stimulation of growth depended on the pancreatropic action of the extracts

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7. Reinhardt, W. O.; Marx, W., and Evans, H. M.: Effect of Pituitary Growth Hormone on the Thymectomized Rat, Proc. Soc. Exper. Biol. & Med. **46**:411-415 (March) 1941.

8. Evans, H. M.: Growth Hormone of the Anterior Lobe of the Pituitary Gland, J. A. M. A. **117**:287-291 (July 26) 1941.

9. Greene, J. A., and Johnston, G. W.: Pituitary Dwarfism: Metabolic Changes by Extracts of Anterior Hypophysis in Primary-Pituitary and in Non-pituitary Dwarfs, J. Clin. Endocrinol. **1**:327-330 (April) 1941.

10. Mirsky, I. A.: The Influence of the Anterior Pituitary Gland on Protein Metabolism, Endocrinology **25**:52-56 (July) 1939.

of the anterior lobe. On the other hand, Marks and Young [11] claimed that although insulin-increasing (pancreatropic) substance accompanied the growth-promoting factor in extracts of anterior pituitary, the two factors were not identical.

Ingalls and Hayes [12] attributed to the adrenal cortex the same role in growth as Mirsky assigned to the pancreas. They stated that atrophy of the adrenal glands, which has been shown to occur after hypophysectomy, may be the major factor in the interruption of growth which ensues; a marked failure of endochondral bone formation, similar to that which follows hypophysectomy, was demonstrated after ablation of the adrenal glands.

Shipley and Long [13] felt that the ketogenic, diabetogenic and growth-promoting hormones might be identical. Greaves and his associates [14] recently suggested that not only the ketogenic but the respiratory quotient–reducing factors were related to the growth hormone.

Clinical Aspects.—Reviews of the clinical syndromes presumably due to disturbances of the growth factor have been presented by Sevringhaus [6] and Wohl.[15] Briefly, these dysfunctions were classified by these authors as follows:

Gigantism: This condition presumably is due to excessive activity of the anterior lobe in stimulating growth during childhood and early adolescence. As Sevringhaus has pointed out, irradiation of the pituitary gland in children with this condition with the view to reducing the stimulation to body growth is not to be recommended because of the possibility of interfering with other functions of the pituitary. In any event, an attempt to limit stature should not be made before the child has reached a height of at least 5 feet (152 cm.), since the excessive rate of growth may cease spontaneously at about that time. Epiphyseal union which is delayed may be hastened by the administration of thyroid, estrogen or androgen. Many physicians, however, do not believe in any treatment for persons whose height is within reasonably normal limits.

11. Marks, H. P., and Young, F. G.: Hypophysis and Pancreatic Insulin, Lancet **1**:493-497 (March 16) 1940.

12. Ingalls, T. H., and Hayes, D. R.: Epiphyseal Growth: Effect of Removal of Adrenal and Pituitary Glands on Epiphyses of Growing Rats, Endocrinology **29**:720-724 (Nov.) 1941.

13. Shipley, R. A., and Long, C. N. H.: Studies on Ketogenic Activity of the Anterior Pituitary: I. Relation of Ketonaemia to Ketonuria in the Rat; II. A Method for the Assay of Ketogenic Activity; III. The Nature of the Ketogenic Principle, Biochem. J. **32**:2242-2256 (Dec.) 1938.

14. Greaves, J. D.; Freiberg, I. K., and Johns, H. E.: Preparation and Assay of Anterior Pituitary Fractions Rich in Ketogenic and Respiratory Quotient-Reducing Substances, J. Biol. Chem. **133**:242-259 (March) 1940.

15. Wohl, M. G.: Diagnosis and Treatment of Anterior Pituitary Disturbances, West. J. Surg. **49**:309-317 (June) 1941.

Acromegaly: Acromegaly presumably is due to excessive secretion of the growth factor after epiphysial union has taken place. If a tumor of the pituitary gland can be demonstrated and disturbances of the visual field exist, surgical intervention is indicated. In those instances in which a tumor is found but disturbances of vision have not occurred, irradiation of the lesion is often employed. A trial of treatment with estrogens has been recommended by some investigators but has not met with encouraging success. Experimentally at least, estrogens have been shown to inhibit function of the anterior lobe. Not infrequently, the process burns itself out spontaneously.

Dwarfism: Underactivity of the growth-promoting hormone of the anterior lobe of the pituitary gland during childhood has been claimed to be the cause of certain types of dwarfism characterized by infantilism, failure of the secondary sex characters to develop, low basal metabolic rate and failure of hair growth. Providing other causes for the failure to grow, such as primary hypothyroidism, can be excluded, treatment with aqueous pituitary extracts containing the growth factor may be employed. Growth-promoting preparations at present are generally made from fresh or acetone-desiccated tissue from the anterior lobe of the pituitary. They usually are standardized by measurement of their capacity for producing growth in young hypophysectomized or normal rats. Although purified, the best preparations of this sort cannot lay claim to being simple homogeneous substances. Because their action is brief, they must be given daily. Evans [8] did not recommend the administration of crude extracts of the anterior lobe because not only must large quantities be employed but such undesirable consequences as gonadotropic and diabetogenic effects may ensue. Sevringhaus [6] advised against the use of desiccated thyroid with a preparation of the anterior lobe of the pituitary containing the growth principle since the former substance tends to hasten epiphyseal closure.

Despite the difficulties encountered in the treatment of this type of patient a considerable number of such dwarfed children have been reported to have improved with treatment. Most observers, however, have been disappointed with the clinical use of growth principle. More extensive clinical use of this factor awaits the preparation of a purified preparation of the specific growth-promoting principle and more convincing evidence, both experimental and clinical, of its activity. Instances have been reported of acceleration of growth following the administration of "gonadotropic" substances.[16]

16. Dorff, G. B.: Chorionic Gonadotropic Effects on Growth in Sexually Underdeveloped Older Boys, Am. J. Dis. Child. **60**:1043-1057 (Nov.) 1940; Rapid Growth in Height Produced by Chorionic Gonadotropin in a Dwarfed, Infantile Identical Twin, J. Clin. Endocrinol. **1**:940-944 (Dec.) 1941. Shelton, E. K.: The Clinical Aspects of Dwarfing, Endocrinology **30**:1000-1014 (June) 1942.

Failure of the Anterior Lobe to Secrete the Growth Principle in Adult Life: Such failure has not been associated with any definite syndrome. The condition known as pituitary cachexia, or Simmonds' disease, usually is assumed to be the result of complete destruction or degeneration of the anterior lobe with failure of all of its functions. We shall discuss this condition in greater detail under a separate heading.

Summary.—In summary, then, we may say that experimental evidence points to a role of primary importance for the anterior lobe of the pituitary in normal growth mechanisms, but it is not established definitely as yet whether a single growth hormone or several factors which influence target organs are concerned. The clinical value of growth-promoting extracts of the anterior lobe of the pituitary gland is even more indefinite, and wide acceptance of these preparations as therapeutic agents of proved activity awaits the presentation of much more evidence than is now at hand.

THE GONADOTROPIC HORMONES OF THE ANTERIOR LOBE

In our discussion of gonadotropins we shall confine ourselves to a consideration of those which are obtained directly from the pituitary gland and those which are presumably of pituitary origin, extracted from the blood and the urine of normal men and women and of women who have undergone the menopause. Those gonadotropins which are found in the body fluids in the presence of living chorionic tissue (during pregnancy) originate from the chorionic cells and not from the anterior lobe of the pituitary gland and do not belong in our discussion. However, it should be noted that these chorionic gonadotropins have been shown to be much more active physiologically than are the available preparations of pituitary gonadotropins. Consequently, they offer much more hope of extensive therapeutic usefulness than do the pituitary factors.

Experimental Aspects.—Several gonadotropins have been reported as being elaborated by the anterior lobe of the pituitary gland, but there is no general agreement as to their identity, with the possible exception of the so-called "follicle-stimulating" and "luteinizing" factors. The evidence for the separate entity of these two factors is not completely convincing.

There can be little doubt, however, that the pituitary gland exerts a powerful influence on the gonads in both sexes and that, in turn, the gonads have definite effects on the anterior lobe. Spaying in the young female animal is followed by cytologic changes in the anterior lobe of the pituitary gland; these changes can be reversed by the administration of estrogens. In addition to the cytologic changes the amount of gonadotropin present in the anterior lobe is increased after castration. Furthermore, administration of estrogens to young female rats produces

luteinization in the ovaries. Doisy [17] was of the opinion that this effect may be due to the release of additional luteinizing principle by the anterior lobe.

In the male animal both functions of the testis, spermatogenic and endocrinous, are induced by, and dependent for maintenance on, the gonadotropins from the anterior lobe of the pituitary.[18] In turn, testicular secretions limit the production by the pituitary gland of gonad-stimulating material. Moore [19] stated that seasonal testicular activity in animals "seems to be a problem of pituitary activity."

The difficulty in clearly separating the actions of each of the gonadotropins of the anterior lobe is largely the result of having to depend for differentiation on biologic tests, which are complicated by lack of distinct end points. Particularly unreliable, in the opinion of Engle and Levin,[20] are those results obtained on intact animals in which their own pituitary glands undoubtedly participated in the experiment. These authors stated that only the hypophysectomized rat or mouse affords standard test conditions.

In the hypophysectomized female rat the purified follicle-stimulating extract produces growth and development of numerous follicles, associated with an increase in ovarian weight. Some investigators have claimed that if it is completely separated from the luteinizing factor, the follicle-stimulating principle does not produce any changes of the type ordinarily attributed to the luteinizing factor. Others have reported that the best preparations of either factor if injected in sufficiently large doses or over sufficiently long periods will induce the changes usually ascribed to the other. Furthermore, by manipulating the rate at which the administered gonadotropin reaches the ovary the reactions ascribed to the luteinizing factor may be made to appear or disappear.

The follicle-stimulating factor has been reported to have a secondary effect, namely, the development of the secondary sex characters, presumably because of the secretion of estrogen by the developing follicles. However, Greep and his co-workers [21] and Shedlovsky and his collabora-

17. Doisy, E. A.: The Estrogenic Substances, J. A. M. A. **116**:501-505 (Feb. 8) 1941.

18. Hamilton, J. B.: Therapeutics of Testicular Dysfunction, J. A. M. A. **116**:1903-1908 (April 26) 1941.

19. Moore, C. R.: Physiology of the Testis, J. A. M. A. **116**:1638-1644 (April 12) 1941.

20. Engle, E. T., and Levin, L.: Gonadotropine of the Anterior Lobe of the Pituitary and of Chorionic Tissue, J. A. M. A. **116**:47-52 (Jan. 4) 1941.

21. Greep, R. O.; van Dyke, H. B., and Chow, B. F.: Separation in Nearly Pure Form of Luteinizing (Interstitial Cell Stimulating) and Follicle-Stimulating (Gametogenic) Hormones of the Pituitary Gland, J. Biol. Chem. **133**:289-290 (March) 1940.

tors [22] have described what they claim to be nearly pure follicle-stimulating substance, which in their experience stimulated follicular growth but did not produce an estrogenic effect, as measured by uterine and vaginal changes.

In the hypophysectomized male rat the follicle-stimulating extract produces a reaction analogous to that in the female animal. The epithelium of the seminiferous tubules is maintained or repaired, and formation of sperm appears. However, the interstitial tissue of the testis remains atrophic both histologically and functionally, as evidenced by the atrophic state of the accessory sex glands, the prostate gland and the seminal vesicles.

Proof of the occurrence of the so-called "luteinizing hormone" as a separate entity is particularly hard to obtain when its effect on the ovary of the rodent is studied. Exponents of the dual hormone theory claim that this factor does not have any effect on the ovary of the hypophysectomized female rat, because luteinizing changes can be produced only in follicles which have already ripened to a certain degree. If both the follicle-stimulating and the luteinizing factors are given simultaneously, luteinization and sometimes ovulation results; the ovarian weight increases beyond the sum of the increases produced by the two substances separately, the so-called "augmentation phenomenon." Those who deny the dual hormone theory point out that certain nonspecific substances (zinc sulfate and egg albumin) have been shown [23] to be more effective in the production of this phenomenon when given in combination with follicle-stimulating substance to a female animal than is the luteinizing substance itself.

A more distinct effect is produced in the hypophysectomized male rat by the luteinizing extract. Its administration results in growth and functional activity of the interstitial cells of the testis, as indicated by their histologic appearance, as well as by the growth and development of the accessory sex glands, the prostate gland and the seminal vesicles, presumably as a result of secretion of androgen. The nonspecific substances mentioned previously have not been shown to be capable of stimulating the effects of the luteinizing substance on the interstitial cells of the testis in the hypophysectomized male rat.

Greep [24] recently has added some evidence in favor of the two hormone theory. He produced parabiosis of a hypophysectomized imma-

22. Shedlovsky, T.; Rothen, A.; Greep, R. O.; van Dyke, H. B., and Chow, B. F.: The Isolation in Pure Form of the Interstitial Cell-Stimulating (Luteinizing) Hormone of the Anterior Lobe of the Pituitary Gland, Science **92**:178-180 (Aug. 23) 1940.

23. Saunders, F. J., and Cole, H. H.: On the Reliability of Present Methods for Characterizing Two Gonadotropic Hormones, Follicle-Stimulator and Luteinizer, Endocrinology **23**:302-317 (Sept.) 1938.

24. Greep, R. O.: Pituitary Function in Parabiotic Triplet Rats, Proc. Soc. Exper. Biol. & Med. **44**:214-217 (May) 1940.

ture male rat and of a hypophysectomized immature female rat with a third rat which had been castrated. Thus a pair of testes and a pair of ovaries were simultaneously subjected to the same gonadotropin in identical dosage. Development of all the testicular elements was noted, whereas only follicular stimulation was found in the ovaries.

Further clarification of the problem of the two gonadotropic hormones awaits the preparation of chemically pure substances, and recent work indicates that we shall not have too long to wait. Data which indicate chemical homogeneity have been reported for at least one preparation of the luteinizing factor by Shedlovsky and associates.[22] Greep and his co-workers [25] have reported the preparation of pure luteinizing principle (metakentrin) and of pure follicle-stimulating principle (thylakentrin). Simpson, Li and Evans [26] have reported on the biologic properties of an interstitial cell–stimulating principle from the pituitary gland. The preparation used was capable of maintaining spermatogenesis and activity of the interstitial cells in the adult hypophysectomized male rat.

Assay of Urinary Gonadotropins.—Urinary gonadotropins can be assayed only by biologic methods the accuracy of which is dependent on careful control of many factors. Several methods are available.[20] Drips and Osterberg [27] have reported that the Frank method for measuring urinary gonadotropins was useful as an adjunct to clinical diagnosis of ovarian dysfunction. In this method a combination of gross examination, including measuring the weight, of the uteri and the ovaries of the test animals with microscopic examination of the ovaries for evidence of follicle stimulation and luteinization is employed. Gustavson and D'Amour [28] stated that the method which depends for its end point on vaginal cornification in the test animal should be recommended most highly.

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25. Greep, R. O.; van Dyke, H. B., and Chow, B. F.: Gonadotropins of the Swine Pituitary: I. Various Biological Effects of Purified Thylakentrin (FSH) and Pure Metakentrin (ICSH), Endocrinology **30**:635-649 (May) 1942. Chow, B. F.; van Dyke, H. B.; Greep, R. O.; Rothen, A., and Shedlovsky, T.: Gonadotropins of the Swine Pituitary: II. Preparation and Biological and Physio-Chemical Characterization of a Protein Apparently Identical with Metakentrin (ICSH), ibid. **30**:650-656 (May) 1942. Chow, B. F.: Gonadotropins of the Swine Pituitary: III. Immunological Specificity of Swine Metakentrin, ibid. **30**: 657-661 (May) 1942.

26. Simpson, M. E.; Li, C. H., and Evans, H. M.: Biological Properties of Pituitary Interstitial-Cell-Stimulating Hormone (ICSH), Endocrinology **30**:969-976 (June) 1942; Comparison of Methods for Standardization of Pituitary Interstitial-Cell-Stimulating Hormone (ICSH), ibid. **30**:977-984 (June) 1942.

27. Drips, D. G., and Osterberg, A. E.: An Evaluation of the Frank Method for the Determination of Prolan (Gonadotropic Principle) in the Urine of Nonpregnant Women, Endocrinology **23**:703-710 (Dec.) 1938.

28. Gustavson, R. G., and D'Amour, F. E.: The Assay of Gonadotropins and of Gonadal Hormones, J. A. M. A. **117**:188-193 (July 19) 1941.

Determination of the urinary content of gonadotropins of human subjects has received wide attention, probably because dysfunctions of the reproductive organs are among the most common endocrine disturbances encountered and because methods of bioassay for these principles are relatively simple. Despite the fact that numerous reports on analyses of the urine for gonadotropins have appeared in the literature in the past few years, it is only recently that reasonably accurate data on normal subjects have been obtained.

Several years ago Katzman and Doisy [29] found that in children little or no gonadotropic substance was excreted until the period just preceding the onset of puberty; at this period appreciable amounts could be found. Witschi and Riley [30] found in assays of 100 pulverized, acetone-dried, human pituitary glands that those of children contained only small quantities of gonadotropic principle.

Earlier observations on normally menstruating women indicated that excretion of gonadotropin was insignificant except during the period between the twelfth and the sixteenth day of the cycle; this peak of excretion was assumed to coincide with ovulation. More recent data, however, indicate that an increased excretion of gonadotropins could be observed at any point during the menstrual cycle, although a consistent increase in output seemed to precede the establishment of the menstrual flow.[31] D'Amour and associates [32] found several different types of cycle on daily tests for urinary gonadotropins during fifty complete menstrual cycles and concluded that either "ovulation may occur more than once during the menstrual cycle or ovulation is not directly dependent on the amount of gonadotropin in circulation."

Heller [33] has reported the results of assays for urinary gonadotropic substance during twenty-two complete menstrual cycles of 19 normal young women. She found that this substance was excreted at low levels throughout the cycle. Cyclic increases in the amounts excreted occurred in all but 1 case. However, the pattern of periodic increased excretion of gonadotropin in the urine varied greatly not only as to time relations but as to the number and the magnitude of the peaks of excretion

29. Katzman, P. A., and Doisy, E. A.: A Quantitative Procedure for Determining Normal Excretion of Prolan, Proc. Soc. Exper. Biol. & Med. **30**:1188-1191 (June) 1933.

30. Witschi, E., and Riley, G. M.: Quantitative Studies on the Hormones of Human Pituitaries, Endocrinology **26**:565-576 (April) 1940.

31. Freed, S. C.: Clinical Significance of Hormone Assays, J. A. M. A. **117**:103-110 (July 12) 1941.

32. D'Amour, F. E.; Funk, D., and Liverman, H.: Daily Gonadotropic Hormone Tests During Fifty Complete Menstrual Cycles, Am. J. Obst. & Gynec. **37**:940-946 (June) 1939.

33. Heller, E. J.: Gonadotropic Hormone: Urine Assays During the Menstrual Cycle in Normal Women, J. Clin. Endocrinol. **1**:813-820 (Oct.) 1941.

observed. She concluded that excretion of gonadotropins did not make a distinct pattern which might be classed as normal. Consequently, she was of the opinion that determinations of urinary gonadotropins would not be of any diagnostic value except in the extremes of gonadal dysfunction.

Although the exact nature of the gonadotropin excreted by normal women has not been established as yet, a limited study by D'Amour [34] indicates that this substance is similar to that excreted after the menopause.

The findings in studies on nonpregnant women with amenorrhea have been more conclusive than those in studies on normally menstruating women. It seems well established that the woman with amenorrhea due to spontaneous ovarian failure or to surgical castration excretes an increased quantity of gonadotropin. Salmon and his associates [35] detected an increase in urinary gonadotropin within three days after ovariectomy. These findings coincide with the report of Witschi and Riley [30] that pituitaries from elderly women and castrated persons showed the highest gonadotropic potency among the human glands studied.

In clinical experience tests for urinary gonadotropin in cases of amenorrhea have proved of value in determining whether the ovary or the pituitary is at fault. If the failure to menstruate is due to failure of the pituitary, little or no gonadotropin will be excreted; if it is due to ovarian failure, gonadotropin will occur in the urine in most instances and in many cases the amount will be increased.

Witschi and Riley reported that during the first period of pregnancy the pituitary rapidly lost its gonadotropic potency; it regained it slowly toward the end of pregnancy and rapidly in the puerperium.

These same authors have reported that in the reproductive age groups the hypophyses of men contained four times more gonadotropic principle than did the glands of nonpregnant women. This report coincides with other reports in the literature which indicate that normal men excrete somewhat larger amounts of gonadotropin than do normal women. However, the excretion in men does not appear to be cyclic. Studies of the nature of this urinary gonadotropin of normal men indicate that it is similar to, or identical with, that excreted by ovariectomized or menopausal women. Although increased amounts of gonadotropin have been shown to be excreted by postclimacteric women, several investiga-

34. D'Amour, F. E.: Qualitative Study of Normal Gonadotropins, Am. J. Physiol. **127**:649-653 (Nov.) 1939.

35. Salmon, U. J.; Geist, S. H., and Walter, R. I.: Inhibitory Effect of Implanted Estrogenic Hormone Crystals upon Post-Menopause and Castration Hypophysis of Women, Proc. Soc. Exper. Biol. & Med. **43**:424-426 (Feb.) 1940.

tors have failed to find increased excretion of this principle in aged men with varying degrees of genital involution.[36]

On the other hand, Hamilton [18] reported that loss of testicular function leads to increased secretion of gonadotropins by the pituitary gland and that determinations of urinary gonadotropin might serve to indicate whether atrophy or underdevelopment of the testis is primarily referable to testicular hyposecretion or is secondary to lesions in the pituitary gland.

Clinical Aspects.—Sevringhaus has presented a summary of the clinical syndromes associated with dysfunctions in the supply of gonadotropins. Briefly, he outlined them about as follows:

Hypersecretion: The only condition associated with excessive amounts of gonadotropins of the anterior lobe of the pituitary body is the female climacteric. Sevringhaus has stated that there is no evidence indicating that the appearance of increased amounts of gonadotropin in the pituitary gland, blood and urine of women undergoing the menopause "has any significance for the comfort or health of the patient." Complete relief of symptoms with the dose of estrogen usually employed, he stated, is not due to inhibition of the secretion of the anterior lobe, since typically high climacteric levels of gonadotropic substance in the urine may remain after clinical improvement has occurred.

Other investigators, however, have contradicted Sevringhaus' opinion on the relation between the excess secretion of gonadotropins by the pituitary gland and the symptoms of the menopause. Kaplan [37] reported that irradiation of the pituitary gland was an effective means of controlling the symptoms of the menopause. He claimed that under such circumstances "functional hyperplasia" of the cells of the anterior lobe existed and that irradiation reduced their activity. Pendergrass, Hodes and Griffith [38] likewise reported beneficial results from irradiation of the pituitary glands of menopausal patients. These observations await confirmation.

Lawrence and Moulyn [39] reported that the presence of excessive urinary gonadotropin was a good guide to the selection of patients who might be expected to respond favorably to estrogen therapy. Only 48 of 100 patients who came to them because of symptoms of menopause

36. Leathem, J. H., and Levin, L.: Gonadotropic Action of Normal Male Urine Extract on Ovaries of Normal and Hypophysectomized Immature Rats and of Immature Mice, Endocrinology **29**:8-17 (July) 1941.

37. Kaplan, I. I.: Irradiation of Brain Tumors at Bellevue Hospital, 1924-1939, Radiology **36**:588-595 (May) 1941.

38. Pendergrass, E. P.; Hodes, P. J., and Griffith, J. Q.: Irradiation of Pituitary Gland in Posterior Lobe Hyperfunction Controlled by Biologic Tests, Am. J. Roentgenol. **46**:673-682 (Nov.) 1941.

39. Lawrence, C. H., and Moulyn, A. C.: The Menopause: Hormonic and Therapeutic Study, New England J. Med. **224**:845-847 (May 15) 1941.

had an excess of urinary gonadotropin; 90 per cent of this group were benefited by the administration of estrogens. Of the remaining 52 patients, who did not have an excess of urinary gonadotropin, only 25 per cent were similarly benefited.

Hypogonadism in the Female: When evidence of primary ovarian dysfunction or of disturbance of ovarian function by some pathologic process elsewhere in the body is lacking, ovarian hypofunction may be assumed to be the result of failure of the anterior lobe of the pituitary gland to secrete gonadotropic substance. However, exact proof of this relation under such circumstances is not possible because of the present limitations in the accuracy of hormone assay.

A wide variety of clinical types of ovarian hypofunction has been described. This is not surprising when the three functions of the ovary, ovulation, production of estrogen and production of progesterone, are considered. The intensity and duration of disturbances of the last two functions may vary widely. Further variables are the time and the magnitude of secretion by the anterior lobe of the pituitary gland of the two gonadotropic substances, the follicle-stimulating and the luteinizing principle.

Stimulation of the ovaries can be produced by the administration of extracts of the anterior lobe of the pituitary gland and also of concentrates from the serum of pregnant mares. Sevringhaus was of the opinion that the optimal time for a course of treatment with these substances is the first two weeks of the menstrual cycle. Interruption of treatment is advisable, since one investigator at least has reported that continuous ovarian stimulation results in polycystic degeneration of the ovarian tissue.[40]

Ornstein [41] recently reported that in 4 cases of the Lorain-Levi type of hypopituitarism with amenorrhea, neither pregnant mare's serum alone nor in combination with gonadotropin from the anterior lobe of the pituitary gland was effective in inducing menstrual bleeding or in maintaining the secondary sex characters. Cyclic uterine bleeding associated with changes in the secondary sex characters was induced in these cases by the continuous administration of estrogen, in the form of pellets of estradiol benzoate implanted subcutaneously, supplemented by regularly spaced periods during which progesterone was administered by mouth.

Hypogonadism in the Male: This may occur as one of three fundamental types, namely, infantilism, adiposogenital dystrophy or cryptor-

40. Buxton, C. L.: The Effects of Certain Gonadotropic Extracts on Anovulatory Cycles and Amenorrhea, Am. J. Obst. & Gynec. **42**:236-241 (Aug.) 1941.

41. Ornstein, E. A.: Management of Primary Amenorrhea in Hypopituitarism, J. Clin. Endocrinol. **1**:899-904 (Nov.) 1941.

chidism. Infantilism, in which the testes fail to grow, has been treated with gonadotropic substances, with varying degrees of success. In cases of so-called "adiposogenital dystrophy," in which in addition to genital immaturity and infantilism there is marked obesity, a dietary regimen alone or in conjunction with gonadotropic therapy may be tried. In many instances a reduction diet alone will produce satisfactory results. Schwarz, Newman and Baum [42] reported that in patients with this disorder the administration of gonadotropic substances did not have any effect on the obesity, even though they induced genital development. Treatment of cryptorchidism usually involves a combination of glandular therapy with surgical procedures. Thompson and Heckel [43] stated that glandular therapy often enables the physician to determine whether operative procedures will be necessary at an early age in the individual case. In their experience chorionic gonadotropin has proved most satisfactory. If mechanical obstruction does not exist, the testis often will descend with glandular therapy alone. If the testis does not descend because of some obstruction, Thompson and Heckel are of the opinion that glandular therapy still serves the useful purpose of enlarging the parts and thus facilitating subsequent surgical procedure. Counseller [44] recommended that surgical treatment be delayed in cases of cryptorchidism until puberty, since in many instances spontaneous descent of the testis will occur at or near that time.

Of the gonadotropic substances available for the treatment of these various "hypogonad states," the chorionic gonadotropin contained in pregnant mare's serum or the gonadotropin in extracts of the anterior lobe of the pituitary, both of which stimulate not only the interstitial but the spermatogenic tissue of the testis, are preferable. Relatively large doses at frequent intervals are desirable.

Summary.—The close relation of the anterior lobe of the pituitary gland to the gonads of males and of females is acknowledged but not yet clearly understood. Urinary assays for excreted gonadotropins are valuable, particularly in the postclimacteric state, in which an excessive excretion may indicate that a favorable response to estrogen therapy will be obtained. Treatment of hypogonadism of human beings of each sex with gonadotropic substances has been given rather extensive trial. As yet the results which may be anticipated in a given instance cannot be predicted with any degree of accuracy.

42. Schwarz, H.; Newman, A. B., and Baum, H.: Pituitary Function in Adiposogenital Dystrophy (Fröhlich), Endocrinology **26**:605-608 (April) 1940.

43. Thompson, W. O., and Heckel, N. J.: Endocrine Treatment of Cryptorchidism, J. A. M. A. **117**:1953-1958 (Dec. 6) 1941.

44. Counseller, V. S.: Ten Years' Experience in Management of Cryptorchidism, J. Urol. **46**:722-731 (Oct.) 1941.

THE LACTOGENIC HORMONE OF THE ANTERIOR LOBE

The mechanism responsible for the control of the initiation of lactation at parturition has long been a mystery. Definite progress was not made in this problem until 1928 and 1929, when Stricker and Grueter [45] announced the discovery of a factor produced by the pituitary (lactogenic principle) which was capable of initiating lactation in animals the mammary glands of which had developed suitably. This work has been amply confirmed. Methods for obtaining the lactogenic principle of the anterior pituitary (lactogen) in relatively pure form have been devised.[46]

Various hypotheses have been advanced to explain the absence of lactation during pregnancy and its initiation after parturition. One which has been widely held is that of Nelson,[47] who suggested that the large amounts of estrogen present during pregnancy suppressed lactation by inhibiting secretion of the lactogenic hormone by the anterior lobe of the pituitary or by direct action on the mammary glands or by both. He and many others have claimed that large doses of estrogen could either diminish or completely suppress lactation in various animals. Meites and Turner,[48] however, expressed doubt that an examination of the literature will support these claims. They pointed out that it has been shown [49] that when large amounts of estrogen are given to lactating rats, a considerable amount of the hormone may be excreted in the milk. Since estrogen is known to have a deleterious effect on growth,[50] conclusions concerning suppression of lactation by estrogens based on decrease of the rate of growth of the young as a criterion of lactation may not be valid. Furthermore, the validity of results obtained by administration of estrogen to human beings may be questioned, since in most of the attempts to inhibit lactation with estrogen and androgen,

45. Stricker, P., and Grueter, F.: Action du lobe antérieur de l'hypophyse sur la montée laiteuse, Compt. rend. Soc. de biol. **99**:1978-1980, 1929; Recherches expérimentales sur les fonctions du lobe antérieur de l'hypophyse: Influence des extraits du lobe antérieur sur l'appareil génital de la lapine et sur la montée laiteusse, Presse méd. **37**:1268-1271 (Sept. 28) 1929.

46. Bergman, A. J.; Houchin, O. B., and Turner, C. W.: Efficiency of Extraction and Separation of Certain A P Hormones, Endocrinology **25**:547-553 (Oct.) 1939.

47. Nelson, W. O.: Endocrine Control of the Mammary Gland, Physiol. Rev. **16**:488-526 (July) 1936.

48. Meites, J., and Turner, C. W.: Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition: I. Can Estrogen Suppress the Lactogenic Hormone of the Pituitary? Endocrinology **30**:711-718 (May) 1942.

49. Walker, S. M., and Stanley, A. J.: Effect of Diethylstilbestrol Dipropionate on Mammary Development and Lactation, Proc. Soc. Exper. Biol. & Med. **48**:50-53 (Oct.) 1941.

50. Nelson, cited by Meites and Turner.[48] Hartman, C. G.; Geschickter, C. F., and Speert, H.: Effect of Continuous Estrogen Administration in Very Large Dosage, Anat. Rec. (supp.) **79**:31 (March) 1941.

the babies were removed from the breast simultaneously with the administration of the hormones. Since the maintenance of lactation depends on the nervous stimulus of sucking, which maintains a high secretion of lactogenic hormone by the pituitary gland,[51] in the nonsuckled breast lactation soon might cease spontaneously without any endocrine treatment. Abarbanel and Goodfriend [52] found in a study of 33 parturient women permitted to nurse their babies during the administration of diethylstilbestrol that doses as high as 1 Gm. failed to inhibit the onset of lactation and as high as 50 to 500 mg. failed to inhibit established lactation. Abarbanel [53] pointed out that the relief of engorgement of the breast with estrogens and androgens was not synonymous with inhibition of lactation. Painful engorgement of the breast is not due to filling of the breast with milk but to lymphatic and venous stasis. Few investigators agree about the degree of suppression of lactation which can be obtained with estrogen.

Meites and Turner [54] in experiments on rats found that the administration of large doses of diethylstilbestrol and testosterone propionate to lactating mother rats for the first six days post partum did not decrease the lactogen content of the pituitary gland but actually increased it; at the same time the amount of milk in the mammary glands was reduced somewhat. Large doses of diethylstilbestrol did not reduce the lactogen content of the pituitary glands of immature and of mature male guinea pigs; actually it was increased. Lewis and Turner [55] found that diethylstilbestrol increased the lactogen content of the pituitary gland of mature spayed rats (female) 226 per cent and even could initiate lactation. Parturient rats which were not suckled in the first week post partum had 50 per cent less lactogen in their pituitary glands than suckled rats, and their mammary glands were practically devoid of milk.[55] Meites and Turner suggested that suppression of lactation in some animals with estrogens and androgens might be due to a decrease in the secretion of hormones of the anterior lobe of the pituitary gland other than lactogen;

51. Meites, J.; Bergman, A. J., and Turner, C. W.: Relation of Size of Litter to A P Lactogen Content of Nursing Rabbit, Proc. Soc. Exper. Biol. & Med. **46**:670-671 (April) 1941.

52. Abarbanel, A. R., and Goodfriend, M. J.: The Effect of Stilbestrol upon Lactation, Am. J. Obst. & Gynec. **40**:1037-1046 (Dec.) 1940.

53. Abarbanel, A. R.: The Effects of Testosterone Propionate, Methyl Testosterone, Anhydro-Oxy-Progesterone and Progesterone upon Lactation in the Nursing Human Being, Am. J. Obst. & Gynec. **42**:110-116 (July) 1941.

54. Meites, J., and Turner, C. W.: Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition: II. Why Lactation Is Not Initiated During Pregnancy, Endocrinology **30**:719-725 (May) 1942.

55. Lewis, A. A., and Turner, C. W.: Effect of Stilbestrol on Lactogenic Content of Pituitary and Mammary Glands of Female Rats, Proc. Soc. Exper. Biol. & Med. **48**:439-443 (Nov.) 1941.

these hormones might influence the yield of milk through their action on the availability of the precursors of milk in the blood.

Meites and Turner [56] explained that copious lactation is not initiated during the latter half of pregnancy in spite of well developed mammary glands because the secretion of lactogenic hormone by the pituitary gland remains at a low level, as low as that in the normal, nonpregnant animal. It is puzzling that during pregnancy, when large amounts of estrogen are present in the circulation, the amount of lactogen in the pituitary should not increase as it does after the administration of estrogen. Meites and Turner concluded that some factor must be present during pregnancy which nullifies the stimulating effect of estrogen on the lactogenic hormone. They suggested that this factor is probably progesterone, which is also present in large amounts during gestation. Experimental evidence indicates that if a proper dose ratio is present between the two hormones, progesterone can prevent the normal effects of estrogen.[56] Meites and Turner obtained confirmatory evidence for this hypothesis in experiments on immature female guinea pigs. Progesterone alone had no effect on the lactogen content of the pituitary gland, and estrone (theelin) N. N. R. alone increased this content. Suitable combinations of the two substances either entirely prevented or reduced the increase in lactogenic hormone which could be obtained with estrone alone. The authors stated that during pregnancy lactation does not occur because the progesterone-estrogen ratio was such that the progesterone overrode the lactogen-stimulating effects of estrogen.

Within two to five days after parturition the lactogenic hormone in the pituitary glands of animals has increased 200 to 400 or more per cent, according to Schilling and Laqueur.[57] The amount of lactogenic principle encountered in the urine of parturient women may be eight to sixteen times as much as can be demonstrated during pregnancy. Peterson [58] has suggested that the posterior lobe of the pituitary gland may be the factor responsible for the increased secretion of lactogen after parturition. Meites and Turner presented evidence to show that solution of posterior pituitary U. S. P. does not increase the lactogen content of the pituitary glands of animals. They stated that estrogen was the inciting factor at parturition which increased the secretion of lactogen and initiated lactation. Undoubtedly, hormones other than lactogen (from the parathyroid glands, pancreas and adrenal glands)

56. Meites, J., and Turner, C. W.: Extraction and Assay of Lactogenic Hormone in Postpartum Urine, J. Clin. Endocrinol. **1**:918-923 (Nov.) 1941.

57. Schilling, W., and Laqueur, G. L.: Thyroid-Ovarian Relations: II. The Effect of Castration and Replacement Therapy on Thyroid, Pituitary, Adrenal and Body Weight in Thyrohyperplastic Albino Rats, Endocrinology **29**:103-107 (July) 1941.

58. Peterson, W. E., cited by Meites and Turner.[59]

exert important supplementary effects on lactation, especially on the precursors of milk. After lactation has been initiated, as mentioned previously, the stimulus of nursing is of prime importance in maintaining lactation, probably through a direct action on the lactogen content of the pituitary.[51]

Low secretion of milk may be due not only to underdevelopment of the breasts but to refractoriness of the pituitary gland to stimulation with estrogen or to insufficient estrogen at the time of parturition.[59] Lactogenic hormone or extracts of the whole pituitary gland have been tried to increase lactation; varying degrees of success have been reported. Diethylstilbestrol has been used in animals to increase production of milk.[49] Moderate amounts of estrogen were found to increase lactation, whereas large doses decreased it.

Meites and Turner suggested that assay of the urine for lactogenic principle might be useful for determining whether low secretion of milk by parturient women was due to failure of secretion of lactogen by the pituitary gland.

Summary.—The extensive work of Meites and Turner and of other investigators has suggested that the lactogenic hormone of the pituitary gland is the factor concerned in both the initiation of lactation at parturition and its maintenance throughout the nursing period. However, the amount of lactogen secreted by the anterior lobe apparently is dependent both on endocrinous and on nervous stimulation. During pregnancy progesterone apparently overrides estrogen in respect to the latter's tendency to stimulate secretion of lactogen; consequently, the large amounts of estrogen in circulation fail to induce copious lactation. After parturition the ratio of progesterone to estrogen is altered, so that the latter exerts a dominant effect on the anterior lobe of the pituitary, stimulating secretion of lactogen, which in turn initiates lactation. The results of attempts to stimulate lactation by administration of lactogenic principle are uncertain.

THE THYROTROPIC HORMONE OF THE ANTERIOR LOBE

As long ago as 1888[60] it was reported that total thyroidectomy resulted in hypertrophy of the pituitary gland in experimental animals. That this stimulation of the pituitary gland, and particularly of its secretion of the thyroid-stimulating (thyrotropic) hormone, occurs among

59. Meites, J., and Turner, C. W.: Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition: III. Can Estrogen Content Account for Precipitous Increase in the Lactogen Content of the Pituitary Following Parturition? Endocrinology **30**:726-733 (May) 1942.

60. Rogowitsch, N.: Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse, Beitr. z. path. Anat. u. z. allg. Path. **4**:453-470, 1889.

human beings is suggested by the work of Means.[61] He found that the amount of thyrotropic principle in the blood and urine was greater in patients with myxedema developing after thyroidectomy than that occurring in the body fluids of normal persons.

A pituitary type of myxedema, however, presumably caused by failure of the pituitary gland to secrete the thyrotropic principle, has been reported by Means, Hertz and Lerman [62] and also by Lerman and Stebbins.[63] In the cases they reported the myxedema-like picture was the predominant feature of primary pituitary cachexia, or Simmonds' disease. The clinical findings in these cases so closely resembled those encountered in patients who have primary hypothyroidism that the true diagnosis was unsuspected until acute adrenocortical insufficiency was precipitated by the administration of desiccated thyroid. At necropsy in 1 of these cases the characteristic changes of Simmonds' disease, including atrophy of the pituitary, the thyroid and the adrenal glands and ovaries, were found. Most authors agree that patients who have Addison's disease tolerate thyroid medication poorly, although Thompson [64] has stated that correcting low basal metabolic rates in patients with this disease with desiccated thyroid produced clinical improvement of the hypometabolism without aggravating the symptoms of adrenocortical insufficiency. His patients, however, were receiving adequate treatment for their Addison's disease at the time they were given the thyroid medication. In the cases of Simmonds' disease in which symptoms of adrenocortical insufficiency developed during treatment with desiccated thyroid, the hypopituitarism had not been recognized previously and hence treatment of the adrenocortical insufficiency had not been given. In 1 case, reported by Lerman and Stebbins, in which this series of complications had developed during thyroid medication, the patient responded well to therapy directed toward the alleviation of the adrenocortical failure.

These same authors pointed out that with the exception of the low basal metabolic rate the signs of hypopituitarism, such as atrophic vaginal mucosa, infantile uterus, loss of libido, amenorrhea, eunuchoid habitus in the male and scanty pubic and axillary hair, point to the pituitary as the source of trouble. The finding of hypotension instead of the normal blood pressure or the hypertension ordinarily present in primary

61. Means, J. H.: Diseases of the Thyroid Gland, New England J. Med. **221**:820-825 (Nov. 23) 1939.

62. Means, J. H.; Hertz, S., and Lerman, J.: The Pituitary Type of Myxedema or Simmonds' Disease Masquerading as Myxedema, Tr. A. Am. Physicians **55**:32-53, 1940.

63. Lerman, J., and Stebbins, H. D.: The Pituitary Type of Myxedema: Further Observations, J. A. M. A. **119**:391-395 (May 30) 1942.

64. Thompson, W. O.: Addison's Disease: Recent Contributions to Treatment, J. Michigan M. Soc. **39**:648-653 (Sept.) 1940.

hypothyroidism should suggest the diagnosis of hypopituitarism. Confirmatory laboratory evidence of hypopituitarism includes a positive result of the salt deprivation test for adrenocortical insufficiency, increased sensitivity to injected insulin, a negative result of the test for follicle-stimulating substance in the urine, low urinary content of the seventeen ketosteroids indicative in the female of activity of the adrenal cortex, and low level of cholesterol in the blood. Treatment of patients with hypopituitarism with pituitary extracts was of no benefit, but a regimen of injections of pregnant mare's serum combined with added salt in the diet and small doses of desiccated thyroid resulted in considerable improvement.

Wilson [65] reported that a considerable percentage of middle-aged women suffering from neuromuscular pains, somnolence, loss of libido, low blood pressure and moderately low basal metabolic rates with increased level of cholesterol in the blood could be relieved by injections of extracts of the anterior lobe of the pituitary.

Lerman [66] reported that the thyrotropic principle of the anterior lobe was capable of producing thyroid hyperplasia and increased basal metabolic rates in animals, presumably by direct effect on the thyroid cells. Starr and Metcoff [67] claimed that a single subcutaneous injection of a preparation of the anterior lobe of the pituitary gland containing thyrotropic principle (antuitrin-T) would result in a significant increase in the mean height of the acinar cells within eight to sixteen hours; the effect persisted at least forty-eight hours after the injection. Belasco and Murlin [68] found that in rats the administration of the thyrotropic factor increased the weight of the thyroid in spite of concomitant loss in body weight. Furthermore, this factor greatly increased the rate of oxygen consumption in the thyroid tissue of old rats. Thyroxin itself, on the contrary, depressed respiration in the thyroid tissues and increased storage of colloid material in the thyroid cells. The authors postulated that this last effect might result in loss of ability of the thyroid tissue to return to activity after cessation of thyroid medication. They suggested that in cases in which the need for thyroid medication was only temporary, intermittent injection of the thyrotropic principle supplemented by doses of desiccated thyroid might be preferable to continuous

65. Wilson, J. A.: A Syndrome Responding to Parenteral Anterior Pituitary Extract, South. Med. & Surg. **103**:370-372 (July) 1941.

66. Lerman, J.: The Physiology of the Thyroid Gland, J. A. M. A. **117**: 349-359 (Aug. 2) 1941.

67. Starr, P., and Metcoff, J.: Rapid Response of Guinea Pig Thyroid to Single Injection of Thyrotropic Hormone, Proc. Soc. Exper. Biol. & Med. **46**: 306-308 (Feb.) 1941.

68. Belasco, I. J., and Murlin, J. R.: Effect of Thyroxin and Thyrotropic Hormone on Basal Metabolism and Thyroid Tissue Respiration of Rats at Various Ages, Endocrinology **28**:145-152 (Feb.) 1941.

thyroid medication alone. Presumably this plan of treatment would facilitate the subsequent resumption of function by the thyroid gland.

Sevringhaus, however, stated that in cases of hypothyroidism it was not possible to obtain sustained thyroid stimulation with thyrotropic principle. Consequently, he did not think that irradiation of the pituitary gland was warranted in cases of hyperthyroidism in an attempt to reduce the amount of thyrotropic substance secreted. Chapman [69] recently has reported that the response of the thyroid gland both of intact and of hypophysectomized animals to inadequate intake of iodine was similar. In each instance the thyroid gland responded to the stimulus of low intake of iodine with an increase in weight, an increase in the height of the acinar epithelium and an increase in vascularity. The author concluded from this evidence that the thyroid gland was able to respond to the stimulus of low intake of iodine in the absence of the pituitary gland.

It has been reported on several occasions in the past and recently confirmed by Uotila [70] that thyroid exerted a depressing effect on the thyrotropic function of the anterior lobe of the pituitary. Means [61] reported that the amount of thyrotropic principle demonstrable in the blood and the urine of hyperthyroid patients was less than that found in normal persons.

Friedgood [71] reviewed the theories concerning the mechanism of exophthalmos in cases of parenchymatous hyperplasia of the thyroid gland. He concluded that edema of the orbital tissues was the most likely explanation and that its production was related to the thyrotropic activity of the anterior lobe of the pituitary gland. In experimental animals injections of extracts of the anterior lobe produced an orbital edema which went through two phases, one of which was reversible and the second of which was irreversible. He suggested that the reversible phase was the type ordinarily encountered in exophthalmic goiter. The irreversible phase is encountered rarely in the early stages of exophthalmic goiter and infrequently as a postoperative complication thereof. Friedgood offered two explanations of the cause of the postoperative orbital edema: (1) withdrawal of the normal inhibitor (thyroid secretion) of excessive secretion of the thyrotropic and a separate principle of unknown nature, the exophthalmos-producing (ophthalmotropic) factor, which probably does not exist as such in the pituitary of a normal

69. Chapman, A.: The Relation of the Thyroid and the Pituitary Glands to Iodine Metabolism, Tr. Am. A. Study Goiter, 1941, pp. 169-175.

70. Uotila, U. U.: The Regulation of Thyrotropic Function by Thyroxin After Pituitary Stalk Section, Endocrinology **26**:129-135 (Jan.) 1940.

71. Friedgood, H. B.: Clinical Applications of Studies in Experimentally Induced Exophthalmos of Anterior Pituitary Origin, J. Clin. Endocrinol. **1**:804-812 (Oct.) 1941.

person, or (*2*) upset of the integrated control of water balance by the thyroid and the pituitary gland. Perhaps the so-called "ophthalmotropic" principle is normally concerned in the maintenance of water balance.

THE ADRENOTROPIC HORMONE OF THE ANTERIOR LOBE

The close relation between the anterior lobe of the pituitary gland and the adrenal cortex has already been mentioned in connection with the "pituitary type of myxedema." In cases of this type atrophy of the adrenal glands with consequent adrenal insufficiency during the life of the patient presumably is caused by failure of the pituitary to secrete an adrenotropic factor.

Stephens [72] reported that in 6 of 7 cases in which clinical evidence of hypopituitarism was found on study with the standard salt deprivation test as outlined by Cutler, Power and Wilder,[73] concentration of chloride in the urine was increased to a degree similar to that which those authors had found characteristic of adrenocortical insufficiency. In 4 of this group of 6 cases symptoms suggestive of acute adrenocortical insufficiency developed during the course of the illness and were relieved promptly by the intravenous administration of salt, dextrose and adrenocortical extract. In 2 cases there was less tendency to excrete an excess of chlorides during the provocative procedure following a regimen of added salt in the diet and injections of adrenocortical extract; in 1 additional case the general clinical appearance of the patient improved considerably on this regimen.

Stephens concluded that the clinical picture of chronic adrenocortical insufficiency frequently accompanied hypopituitarism; he [74] recommended that the salt deprivation test for the former be employed as a precautionary measure prior to the administration of thyroid or surgical procedures in all cases in which pituitary failure is suspected.

In contrast to the hypofunction of the adrenal cortex in hypopituitarism, or Simmonds' disease, is the hyperfunctioning of the adrenal cortex which, according to Albright and his collaborators,[75] is always

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72. Stephens, D. J.: Chloride Excretion in Hypopituitarism with Reference to Adrenocortical Function, Am. J. M. Sc. **199**:67-75 (Jan.) 1940.

73. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Sodium Chloride and Potassium in the Blood Plasma and Urine of Patients with Addison's Disease: Their Diagnostic Significance, Proc. Staff Meet., Mayo Clin. **13**:244-249 (April 20) 1938.

74. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, J. Clin. Endocrinol. **1**: 109-112 (Feb.) 1941.

75. Albright, F.; Parson, W., and Bloomberg, E.: Therapy in Cushing's Syndrome: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis; Results of Treatment with Testosterone Propionate, J. Clin. Endocrinol. **1**:375-384 (May) 1941.

associated with the Cushing syndrome. This syndrome, which may be associated with a basophilic adenoma of the pituitary gland or with an adenoma or carcinoma of the adrenal cortex, will be discussed under a separate heading.

No clinical trials of extracts of the anterior lobe of the pituitary gland containing the adrenotropic factor have been reported in the recent literature.

SIMMONDS' DISEASE, OR PITUITARY CACHEXIA

Many instances of failure of the pituitary gland, or Simmonds' disease, have been reported, but no general agreement concerning its causation or its treatment has been reached. This diversity of opinion is due partly to the fact that occasionally typical clinical cases may be encountered in which necropsy fails to reveal pathologic changes in the pituitary; the opposite also is found; that is, complete destruction of the pituitary may be discovered at necropsy in a case in which few or none of the phenomena generally associated with pituitary cachexia had been exhibited. Further confusion is added by the fact that Addison's disease rarely and anorexia nervosa frequently simulate closely the clinical appearance of true pituitary cachexia.

Escamilla and Lisser [76] recently published a statistical analysis of 595 cases of Simmonds' disease, in 101 of which the diagnosis was proved by pathologic examination. They included in their paper an excellent review of the literature to date. These authors considered four cardinal symptoms to be necessary for a clinical diagnosis of Simmonds' disease, namely: (1) loss of weight; (2) loss of sexual function; (3) asthenia, and (4) a low basal metabolic rate (less than — 20 per cent).

Escamilla and Lisser's study revealed that the disease was more frequently encountered among women than men, during adult life. Of particular etiologic significance they considered (1) infectious processes (in 13 of the 101 pathologically confirmed cases the onset of the disease apparently followed or coincided with an infectious process) and (2) pregnancy (which apparently was of even greater etiologic significance). Pregnancy occurred just before the onset of symptoms in 42 per cent of 67 pathologically verified cases of the disease among women. In more than half of these instances abnormal hemorrhage occurred immediately after parturition. The pituitary is known to undergo rapid involution post partum, presumably, in part at least, because of a reduction in the blood flow to the gland. The authors postulated that if this reduction in blood flow were aggravated by a sudden fall in blood pressure due to hemorrhage, thrombi might be precipitated in the sinuses of the gland and infarction and necrosis might follow.

76. Escamilla, R. F., and Lisser, H.: Simmonds's Disease: A Clinical Study with Review of the Literature; Differentiation from Anorexia Nervosa by Statistical Analysis of Five Hundred and Ninety-Five Cases, One Hundred and One of Which Were Proved Pathologically, J. Clin. Endocrinol. **2**:65-96 (Feb.) 1942.

Pituitary cachexia usually ends fatally, although it may run a long course. In Escamilla and Lisser's series the course was from thirty to forty years. These authors doubted whether true pituitary cachexia can be benefited materially by any form of therapy, for although "the duration of life may have been prolonged in a few of these patients by glandular therapy, . . . in many of them, it was of no help whatever." However, in 60 per cent of cases in which the clinical picture was typical, although pathologic investigation was not carried out, a variety of endocrine products (pituitary extracts; thyroid; adrenal, ovarian and testicular extracts; insulin, and so forth) produced remarkable improvement. In these cases unintentional psychotherapy, spontaneous resumption of pituitary function or coincidence may have accounted for some of the improvement seen. Indeed, marked improvement in these cases suggests a diagnosis of anorexia nervosa, particularly when the picture is predominantly that of marked loss of weight and low basal metabolic rate in a young unmarried and nulliparous female.

Smith [77] has suggested two diagnostic procedures which may be helpful in the differentiation of anorexia nervosa and pituitary cachexia. He employed a combination of the insulin tolerance test and an assay of the urine for seventeen ketosteroids in making the distinction. In pituitary cachexia a characteristic curve was obtained after injection of insulin; after a normal initial decrease in blood sugar, a failure or a delay in the usual spontaneous return of the blood sugar to normal occurred. Since approximately half of the patients with conditions other than primary pituitary cachexia (such as Addison's disease, severe hepatic disease and severe malnutrition) may have insulin tolerance curves of similar form, assay of the urine for the seventeen ketosteroids is a necessary adjunct to diagnosis. In all but 1 of 10 cases of Simmonds' disease this assay yielded negative results, whereas in cases of other conditions normal or near normal results were obtained.

CUSHING'S SYNDROME

Aside from the reports of additional cases of this syndrome, few contributions to the subject have been made in the recent literature.

Albright and his associates [78] claimed that in Cushing's syndrome many of the symptoms and signs were due to hyperglyconeogenesis from body proteins, which produced not only a decreased tolerance for dextrose but a decreased availability of amino acids with which to build protein. They stated that this lack of protein accounted for insulin resistance, mild diabetes, muscular weakness, amenorrhea, impotence, atrophy of the skin and of the walls of the small vessel and osteoporosis.

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77. Fraser, R., and Smith, P. H.: Simmonds's Disease or Panhypopituitarism (Anterior): Its Clinical Diagnosis by the Combined Use of Two Objective Tests, Quart. J. Med. **10**:297-330 (Oct.) 1941.

Since testosterone propionate has been shown to promote nitrogen storage, Albright treated patients suffering from Cushing's syndrome with this compound. A prompt retention of nitrogen and phosphorus and reestablishment of a positive calcium balance resulted. Associated with the nitrogen retention was a decrease in thinness of the skin, increased muscular strength and loss of easy "bruisability." Treatment of 2 patients with estradiol benzoate did not produce such beneficial results. Progesterone had a slightly favorable effect in 1 instance but generally speaking was inferior to testosterone.

Rakoff and co-workers [78] reported that in 1 case of far advanced Cushing's syndrome treatment with diethylstilbestrol produced clinical improvement within a short time. The blood pressure and the amount of androgens excreted were reduced; however, a preexisting glycosuria was aggravated. In a second case in which the disease was less severe, the improvement under diethylstilbestrol therapy was progressive over a period of one year, during which the patient was under observation. The menses were resumed, and a reduction in body weight and a marked lessening of hirsutism occurred.

MISCELLANEOUS FACTORS OF THE ANTERIOR LOBE

In addition to the hormones of the anterior lobe of the pituitary gland which we have discussed in detail, several other factors have been reported in the literature. Since work on these principles is still in the experimental phase and their clinical relations have not become established, we shall mention only a few of them briefly.

No recent reports have appeared in the literature concerning the status of the parathyrotropic principle which several years ago was reported to be present in the urine of patients with hyperplasia of the parathyroid glands.

Houchin and Turner [79] reported that in experimental animals the injection of certain extracts of the anterior lobe resulted in a marked rise in the secretion of bile which persisted over a period of four to eight hours.

Levin and Leathem [80] found that hypophysectomy in rats resulted in a fall in serum albumin and a rise in serum globulin. These changes were reproduced to only a slight degree by simple inanition of similar intensity and duration. Administration of thyroid prevented the increase in serum globulin, while administration of adrenal cortical extract or desoxycorticosterone acetate prevented the decrease in serum albumin.

78. Rakoff, A. E.; Cantarow, A., and Paschkis, K. E.: Cushing's Syndrome: Two Cases Treated with Stilbestrol, J. Clin. Endocrinol. **1**:912-915 (Nov.) 1941.

79. Houchin, O. B., and Turner, C. W.: The Relation of the Anterior Pituitary to Bile Production, Endocrinology **26**:821-823 (May) 1940.

80. Levin, L., and Leathem, J. H.: The Relation of the Pituitary, Thyroid and Adrenal Glands to the Maintenance of Normal Serum Albumin and Globulin Levels, Am. J. Physiol. **136**:306-313 (April) 1942.

The authors concluded that hypophysectomy resulted in alteration both in the serum albumin and in the serum globulin because of removal of the adrenotropic and the thyrotropic hormones, respectively.

Sutton [81] reported 6 cases of advanced pellagra in which either great improvement or complete recovery occurred from injections of extracts of anterior pituitary. Stopping the administration of the pituitary extract resulted in relapses. Furthermore, administration of pituitary extracts produced marked clinical improvement in alcoholic polyneuritis and cheilosis even in the absence of an adequate intake of the vitamin B complex. In some cases of achylia in association with pellagra treatment with anterior pituitary extract resulted in a return of gastric secretion. Purified extracts containing the gonadotropic or the growth principle were almost as effective as the whole pituitary extract. In some of the cases of pellagra recovery took place after the patient had failed to respond to therapy with niacin (nicotinic acid), riboflavin, liver administered parenterally and an adequate diet. The author concluded that the hormone or hormones of the anterior lobe of the pituitary gland may be essential to the utilization of the vitamin B complex.

RELATION OF THE ANTERIOR LOBE OF THE PITUITARY GLAND TO METABOLISM

Metabolism of Carbohydrates.—Since the work of Houssay in 1924 the importance of the relation of the anterior lobe of the pituitary gland to carbohydrate metabolism has received much emphasis. Young [82]; Dohan, Fish and Lukens [83]; and Marks and Young,[11] and others have contributed largely to the present knowledge of this subject. Because most of the work on this phase of pituitary physiology has been covered in reviews of metabolism for 1940 [84] and 1941,[85] we shall include in this paper mention only of the most recent contributions to the subject.

Houssay and his co-workers [86] recently have reviewed all of the previous work in his laboratory on relations of the anterior lobe of

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81. Sutton, D. C.: Interrelation Between Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, South. M. J. **34**:48-51 (Jan.) 1941.

82. Young, F. G.: Anterior Pituitary Fractions and Carbohydrate Metabolism: I. The Preparation and Properties of Diabetogenic Extracts, J. Endocrinol. **1**: 339-355 (Nov.) 1939; The Pituitary Gland and Carbohydrate Metabolism, Endocrinology **26**:345-351 (Feb.) 1940.

83. Dohan, F. C.; Fish, C. A., and Lukens, F. D. W.: Induction and Course of Permanent Diabetes Produced by Anterior Pituitary Extract, Endocrinology **28**:341-357 (March) 1941.

84. Rynearson, E. H., and Hildebrand, A. G.: Metabolism and Diabetes: Review of Certain Recent Contributions, Arch. Int. Med. **68**:134-175 (July) 1941.

85. Hildebrand, A. G., and Rynearson, E. H.: Diseases of Metabolism: Review of Certain Recent Contributions, Arch. Int. Med. **69**:344-365 (Feb.) 1942.

86. Houssay, B. A.; Foglia, V. G.; Smyth, F. S.; Rietti, C. T., and Houssay, A. B.: The Hypophysis and Secretion of Insulin, J. Exper. Med. **75**:547-566 (May) 1942.

the pituitary to carbohydrate metabolism. They concluded that the rise in the level of the sugar in the blood which was observed to occur within the first few days after the administration of extracts of the anterior lobe to animals had been started was due to extrapancreatic activity. Along with this effect the pituitary extracts damaged the islet cells of the pancreas; of course, this damage would be aggravated by the initial hyperglycemia. Damage to the islet cells might become so severe that their ability to secrete insulin would remain diminished after cessation of the injections of pituitary extract. In these instances, persistent diabetes mellitus would result. Houssay found that in many instances the diabetes gradually disappeared, along with reversal of the histologic changes which had been produced in the islet cells. However, in some instances, a permanent diabetic state was established. In these animals extensive degenerative changes were encountered in the pancreatic islands, particularly in the beta type of cell.

Lukens and Dohan [87] also have reviewed the subject of pituitary diabetes in the cat; they confirmed Houssay's observations as to the mode of action of the extracts of the anterior lobe of the pituitary gland. They reported that recovery in these animals took place under dietary and insulin therapy.

A so-called "contrainsular" hormone has been claimed to antagonize the action of insulin. Himsworth [88] suggested that a substance such as the diabetogenic or contrainsular factor might be responsible for the resistance to insulin sometimes encountered in cases of diabetes mellitus.

Recently some doubts have appeared concerning the existence of a "pancreatropic" factor secreted by the anterior lobe of the pituitary gland, which previously had been reported to increase secretion of insulin by the pancreas. Marks and Young [11] have reported that certain extracts of the anterior lobe would increase the insulin content of the rat pancreas to almost twice normal values. Collip [89] claimed that a primary alcoholic extract of the anterior lobe "has a profound effect upon carbohydrate metabolism" when administered orally to diabetic organisms. By this statement he meant that oral administration of this extract was capable of reducing the levels of blood sugar in a fasting organism and also the total daily requirement of insulin in some cases of diabetes mellitus; in fasting animals he produced a lowering of the level of sugar in specimens of blood taken after the oral administration of the extract. He suggested that this effect on carbohydrate metabolism was mediated by a "pan-

87. Lukens, F. D. W., and Dohan, F. C.: Pituitary Diabetes in the Cat: Recovery Following Insulin or Dietary Treatment, Endocrinology **30**:175-202 (Feb.) 1942.

88. Himsworth, H. P.: The Mechanism of Diabetes Mellitus, Lancet **2**:65-68 (July 8) 1930.

89. Collip, J. B.: An Anti-Diabetogenic Effect of a Primary Alcoholic Extract of Pituitary Tissue Administered Orally, Canad. M. A. J. **42**:109-113 (Feb.) 1940.

creatropic" action on the islets of Langerhans. Lawrence and Young [90] failed to substantiate this claim in studies on diabetic persons and on dogs made permanently diabetic by injection of extracts of the anterior lobe. Marks and Young [91] did not find Collip's extract "significantly pancreatropic when administered to rats either by subcutaneous injection or by mouth." Although these same investigators found various crude pituitary extracts capable of increasing the insulin content of the rat pancreas, they stated that the pancreatropic factor was "probably not a hormone" and not identical with the lactogenic, the gonadotropic, the thyrotropic or the glycotropic substance.

Houssay and his co-workers [86] reported that the pancreas of hypophysectomized dogs was capable of normal secretion of insulin. Griffiths [92] claimed that in hypophysectomized rats, both the decrease in pancreatic content of insulin postoperatively and the increase in this content after the administration of extracts of the anterior lobe of the pituitary were proportional, respectively, to the loss of body weight, on the one hand, and to the gain in body weight, on the other. He discounted the presence of a specific insulin-increasing hormone in the anterior lobe of the pituitary gland.

Metabolism of Proteins and Fats.—Little of significance has been added to the literature concerning the influence of the anterior lobe of the pituitary on the metabolism of fats and proteins.

The more recent work on the relation of the anterior lobe to protein metabolism in connection with body growth has already been discussed.

The consensus seems to be that extracts of the anterior lobe are capable of inducing nitrogen retention in the body tissues of animals receiving injections of this material.[93]

Several investigators in the past have reported that certain extracts of anterior pituitary had marked effects on fat metabolism of experimental animals. Sykes, Meuleman and Huffman [94] recently reported that a preparation of anterior lobe possessing marked liver-fat activity affected fat production of the mammary glands of 3 dairy cows. Both the total fat produced and the percentage of fat of the milk were increased.

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90. Lawrence, R. D., and Young, F. G.: Oral Anterior Pituitary Extract (Collip) in Diabetes, Lancet **2**:709-710 (Dec. 7) 1940.

91. Marks, H. P., and Young, F. G.: Pancreotropic Factor of the Anterior Pituitary Lobe, Lancet **2**:710-712 (Dec. 7) 1940.

92. Griffiths, M.: The Influence of Anterior Pituitary Extract on the Insulin Content of the Pancreas of the Hypophysectomized Rat, J. Physiol. **100**:104-111 (Aug. 11) 1941.

93. Cuthbertson, D. P.; Webster, T. A., and Young, F. G.: Anterior Pituitary Gland and Protein Metabolism: I. Nitrogen-Retaining Action of Anterior Lobe Extracts, J. Endocrinol. **2**:459-467 (Sept.) 1941.

94. Sykes, J. F.; Meuleman, W. L., and Huffman, C. F.: Changes in the Fat Percentage and Fat Yield of Dairy Cows with Injections of an Anterior Pituitary Preparation, Endocrinology **30**:217-220 (Feb.) 1942.

THE POSTERIOR LOBE OF THE PITUITARY

The neurohypophysis consists of three poorly defined regions: (1) the neural lobe; (2) the infundibular stem, and (3) the median eminence. Weaver and Bucy [95] have discussed the anatomic relations of the posterior lobe in detail.

The so-called "posterior lobe hormones" include the pressor, antidiuretic, oxytocic and melanophore-depressing principles. The pressor, antidiuretic and oxytocic hormones arise from the intrinsic elements of the neurohypophysis, the pituicytes.[96]

While the pituicytes are regarded as secretory elements, the function of the unmyelinated nerve fibers present is not clear. There is evidence that they may be concerned in a reflex connection between the vagus and the supraopticohypophyseal tract.[97]

Recent work has renewed interest in studies of the hormones of the posterior lobe in the body fluids. Gilman and Goodman [98] several years ago demonstrated that rats deprived of water would excrete the antidiuretic principle of the posterior lobe. Recently considerable work has been done on the presence of the antidiuretic and the pressor principle in the body fluids, particularly in connection with their detection in eclampsia, hypertension and certain other diseases. Attempts have been made to associate these conditions with hypersecretion of the posterior lobe of the pituitary. For example, it has been shown that in eclamptic or preeclamptic patients therapeutic doses of preparations of the posterior lobe would produce an unusually marked rise in blood pressure and a concurrent decrease in the volume of urine. This observation has been interpreted to mean either that these patients already had an excessive amount of principles from the posterior lobe in circulation or that they were hypersensitive to them or possibly both.

Variability in the results obtained in assays of the blood and urine of these patients for factors of the posterior lobe has made the clinical applicability of these studies doubtful. Teel and Reid [99] reported that concentrates of urine from women with eclampsia or preeclampsia had marked antidiuretic effects when injected into rats. Concentrates of

95. Weaver, T. A., Jr., and Bucy, P. C.: The Anatomical Relationships of the Hypophysial Stem and Median Eminence, Endocrinology **27**:227-235 (Aug.) 1940.

96. Geiling, E. M. K., and Oldham, F. K.: The Neurohypophysis, J. A. M. A. **116**:302-312 (Jan. 25) 1941.

97. Sattler, D. G.: Vago-Neurohypophysial Pressor Reflex, Proc. Soc. Exper. Biol. & Med. **44**:82-86 (May) 1940.

98. Gilman, A., and Goodman, L.: The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, J. Physiol. **90**:113-124 (July 15) 1937.

99. Teel, H. M., and Reid, D. E.: Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, Endocrinology **24**:297-310 (March) 1939.

urine from normal pregnant women did not have such effect unless the patient was deprived of water; then she would excrete antidiuretic substance. Ham [100] likewise has found an antidiuretic substance in the urine of women in eclampsia. Mukherjee [101] studied the effect of the blood ultrafiltrates obtained in 50 unselected cases of toxemia during pregnancy on the melanophoric, antidiuretic and vasopressor responses in animals. The blood filtrates from normal women failed to result in the "triple response" to any significant degree. The blood filtrates from patients with toxemia had the capacity to produce all three reactions. Mukherjee concluded that the concentration of posterior pituitary hormone in the circulation of patients who had toxemia was increased and also possibly these patients were hypersensitive to this hormone.

In favor of this suggestion that a hyperfunctioning posterior lobe of the pituitary gland might be a potent factor in the production of eclampsia too are these facts: 1. Hypertension is characteristic of eclampsia, and extracts of the posterior lobe are known to have vasopressor effects. 2. The blood volume in eclampsia has been shown to be low,[102] and this effect has been reproduced in animals by the injection of pitressin in pressor dosage.[103] The blood volume in normal pregnant women is high.[103]

On the other hand, in women dying of eclampsia, the renal findings are striking and the pituitary changes difficult to evaluate.[104] Selye and Bassett [105] have pointed out that even though urine and blood of pregnant women contain an antidiuretic substance, this substance is not necessarily derived from the posterior lobe of the pituitary; estrogens, androgens and progesterone may produce antidiuresis. Ham [100] found this antidiuretic substance in normal pregnant women, as well as in eclamptic women, as have other investigators.[103]

Finally, the recent work of Smith and Smith,[106] who found increased gonadotropic substances from the anterior lobe of the pituitary in the

100. Ham, G. C., cited by Griffith, Kimbrough, Corbit and Roberts.[104]

101. Mukherjee, C.: Posterior Pituitary Factor in the Toxemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. **48**:580-609 (Oct.) 1941.

102. Dieckmann, W. J., and Kramer, S.: Edema in Pre-Eclampsia and Eclampsia, Am. J. Obst. & Gynec **41**:1-16 (Jan.) 1941.

103. Griffith, J. Q., Jr.; Corbit, H. O.; Rutherford, R. B., and Lindauer, M. A.: Studies of Criteria for Classification of Arterial Hypertension: V. Types of Hypertension Associated with the Presence of Posterior Pituitary Substance, Am. Heart J. **21**:77-89 (Jan.) 1941.

104. Griffith, J. Q., Jr.; Kimbrough, R. A., Jr.; Corbit, H. O., and Roberts, E.: A Study of the Antidiuretic Factor Occurring in Normal Pregnancy, and the Experimental Production of an Apparently Similar Factor in Nonpregnant Animals, Endocrinology **30**:542-550 (April) 1942.

105. Selye, H., and Bassett, L.: Effect of Desoxycorticosterone and Testosterone on Water and Chloride Metabolism, Proc. Soc. Exper. Biol. & Med. **45**: 272-277 (Oct.) 1940.

106. Smith, G. V. S., and Smith, O. W.: The Anterior Pituitary-Like Hormone in Late Pregnancy Toxemia, Am. J. Obst. & Gynec. **38**:618-624 (Oct.) 1939.

blood and urine of eclamptic patients, directs attention away from the posterior lobe.

Although several commercial preparations of the posterior lobe are available for clinical use, as yet none of the active principles has been isolated as chemically pure entities. Two fractions, pitressin and pitocin, have been separated in a highly purified state from pituitary extracts. Geiling and Oldham [96] have reviewed the present knowledge of the chemical properties of these substances in detail.

Some investigators have expressed the belief that the two factors exist as separate entities in the natural state. However, Rosenfeld [107] in recent studies of their sedimentation properties in the ultracentrifuge found evidence to indicate that the pressor and the oxytocic principle exist normally as relatively large molecules, which are broken down to smaller, physiologically active products by the ordinary methods of chemical extraction.

Briefly, pitressin elicits cardiovascular, respiratory, renal (diuretic-antidiuretic), intestinal and certain metabolic effects on oxygen consumption; pitocin elicits the oxytocic action. Both substances act as antagonists to insulin and produce hyperglycemia.

Clinically, the widest use of extracts of the posterior lobe is in connection with parturition and in the treatment of diabetes insipidus.

The response of the pregnant uterus to preparations of the posterior lobe depends largely on the nature of that ovarian, placental or anterior pituitary hormone the influence of which is predominant at the time of injection. During early pregnancy the human uterus does not respond to pitocin, presumably because of the inhibitory effect on luteal secretion. Later the reactivity of the uterine musculature to pitocin returns, probably because the estrogens render the uterus more responsive. During parturition the uterus is responsive, and it is at this time that posterior pituitary extracts have been used most extensively, principally for the control of postpartum bleeding in the third stage of labor. Its use during the first and the second stage of labor is not recommended, since rupture of the uterus, fetal asphyxia, fetal death, laceration of the cervix, secondary atony of the uterus and even maternal cardiac death from overexertion have been reported.[108] Extracts of the posterior lobe are useful also in the prevention or control of hemorrhage during abortion.

Both clinical and experimental studies support the view that diabetes insipidus is due to loss or diminution in the antidiuretic factor of the

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107. Rosenfeld, M.: The Native Hormones of the Posterior Pituitary Gland: The Pressor and Oxytocic Principles, Bull. Johns Hopkins Hosp. **66**:398-403 (June) 1940.

108. DeLee, J. B.: The Use of Solution of Posterior Pituitary in Modern Obstetrics, J. A. M. A. **115**:1320-1324 (Oct. 19) 1940.

posterior lobe.[109] The anterior lobe likewise plays a role in water metabolism, possibly secreting a diuretic substance, even though a specific diuretic factor has not been isolated from the anterior lobe. Complete hypophysectomy results only in transient diabetes insipidus, since the presence of a functioning anterior lobe, as well as inactivation of the posterior lobe, is essential for the maintenance of permanent maximal diabetes insipidus.[110] Administration of extracts of anterior pituitary to hypophysectomized rats already recovered from the initial postoperative diabetes insipidus again resulted in diabetes insipidus.

Although nasal insufflation of dry pituitary powder has been used successfully in the treatment of diabetes insipidus, attempts have been made to prolong the action of parenterally administered preparations by giving them in oil or with zinc sulfate.[111] Thorn and Stein[112] reported that a single injection of pitressin tannate in oil was effective in controlling polydipsia and polyuria for twenty-four to forty-eight hours in 3 cases of diabetes insipidus. They warned against overdosage because of the danger of water intoxication.

Total thyroidectomy has relieved diabetes insipidus in experimental animals[113] and in human beings. Blotner and Cutler[114] reported that thyroidectomy produced a marked and persistent (for five years at least) improvement in both the diabetes insipidus and the Parkinson's disease of 2 young men whose symptoms followed encephalitis. However, in 1 case in which diabetes insipidus was considered idiopathic, thyroidectomy did not result in any benefit.

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109. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, Endocrinology **26**:801-806 (May) 1940. Dandy, W. E.: Section of the Human Hypophysial Stalk: Its Relation to Diabetes Insipidus and Hypophysial Functions, J. A. M. A. **114**:312-316 (Jan. 27) 1940.

110. Schweizer, M.; Gaunt, R.; Zinken, N., and Nelson, W. O.: The Role of the Adrenal Cortex and the Anterior Pituitary in Diabetes Insipidus, Am. J. Physiol. **132**:141-149 (Feb.) 1941.

111. Greene, J. A., and January, L. E.: Diabetes Insipidus Treated by the Subcutaneous Administration of a Suspension of Pitressin Tannate in Oil, J. A. M. A. **115**:1183-1185 (Oct. 5) 1940. Stephens, D. J.: Zinc Salts and Oil in Prolongation of Therapeutic Effect of Pitressin in Experimental Diabetes Insipidus, Proc. Soc. Exper. Biol. & Med. **44**:240-241 (May) 1940.

112. Thorn, G. W., and Stein, K. E.: Pitressin Tannate Therapy in Diabetes Insipidus, J. Clin. Endocrinol. **1**:680-687 (Aug.) 1941.

113. Mahoney, W., and Sheelan, D.: The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, Am. J. Physiol. **112**:250-255 (June) 1935.

114. Blotner, H., and Cutler, E. C.: Total Thyroidectomy in the Treatment of Diabetes Insipidus, J. A. M. A. **116**:2739-2745 (June 21) 1941.

THE ANTIHORMONES

The so-called "antihormones," first described by Collip and Anderson [115] in 1934, deserve brief mention.

Several investigators [116] have reported that in animals treated with thyrotropic substance first an increased basal metabolic rate and subsequently hypothyroidism occurred. At the latter stage the blood serum of the experimental animals was found to confer "immunity" to the effect of the thyrotropic principle when injected into other animals; that is, the animals were made refractory to the thyrotropic principle. After several months without injections of pituitary extracts the refractory animals again became susceptible to the thyrotropic principle. Such an antihormone effect also has been shown to develop toward the lactogenic,[117] the gonadotropic [118] and other pituitary factors. Because of the apparent transmissibility of immunity from a treated animal to an untreated one, given serum from the former, the refractoriness which develops in experimental animals receiving injections of pituitary extracts has been assumed to represent a true immune reaction due to the formation of antibodies. Thompson, Collip and Selye [117] have reported that the serum containing the "antihormone" (antithyrotropic factor) developing in treated animals was specific for the species of animal from which the pituitary extract was prepared; that is, animals rendered refractory to material from the pituitary gland of sheep still would respond to material from the pituitary gland of pigs.

Clinical evidence does not lend support to the antihormone theory. In the first place, human subjects do not become refractory to long-continued therapy with any of several substances, including thyroid extract, insulin and adrenal cortical extract. In the second place, Thompson and his associates [117] have shown that the serum of animals which have become refractory to the thyrotropic principle will reduce the basal metabolic

115. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, Lancet **1**:76-78 (Jan. 13) 1934.

116. Werner, S. C.: Antibody Nature of Refractoriness to Injections of Hypophyseal Extracts Containing Thyrotropic Hormone, Proc. Soc. Exper. Biol. & Med. **34**:392-394 (April) 1936. Harington, C. R., and Rowlands, I. W.: Fractionation of Antithyrotropic and Antigonadotropic Sera, Biochem. J. **31**:2049-2054 (Nov.) 1937. Loeb, L., and Friedman, H.: Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, Proc. Soc. Exper. Biol. & Med. **29**:172-174 (Nov.) 1931. Cutting, W. C.; Robson, G. B., and Emerson, K., Jr.: Refractoriness from Pituitary Thyrotropic Extracts, Endocrinology **24**:739-740 (May) 1939.

117. Thompson, D. L.; Collip, J. B., and Selye, H.: The Anti-Hormones, J. A. M. A. **116**:132-136 (Jan. 11) 1941.

118. Meyer, R. K.; Kupperman, H. S., and Finerty, J. C.: Increase in Gonadotropic Content of Pituitary Glands of Female Rats Treated with Antigonadotropic Serum, Endocrinology **30**:662-666 (May) 1942.

rate of recipient animals, as well as prevent the usual rise in the basal metabolic rate following the administration of the thyrotropic principle. If the latter phenomenon were due to specific antithyrotropic immune bodies, the antiserum should not be capable of reducing basal metabolic rates. Furthermore, "antihormones" have been reported to be present in the serums of untreated animals and of normal human subjects. Thompson and his associates have raised the question as to whether the "antihormones" are true immune bodies or are normal constituents of the serum. Fellows Nutting,[119] however, has denied that human serum normally contains a substance which exerts an inhibitory effect on anterior pituitary extract of human beings when both are injected into experimental animals.

Rutherford and Griffith [120] reported a case in which a patient experienced recurrent episodes of polyuria and polydipsia without glycosuria after subtotal thyroidectomy. This patient was observed during one such episode; his serum when injected in animals rendered them refractory to the usual antidiuretic effect of extracts of posterior pituitary. During the period of spontaneous recovery from the attack the patient's serum contained an excessive quantity of an antidiuretic factor. The authors did not find any pitressin-inhibiting substance in the serums of 2 patients who had chronic diabetes insipidus.

PITUITARY PREPARATIONS

Experimental preparations of the active principles of the anterior lobe have been developed in which those principles are present in relatively pure form. Among these substances which have been prepared in highly potent and only minimally contaminated form are the lactogenic, the growth-promoting, the thyrotropic and the adrenotropic factor. Although potent gonadotropic substances have been isolated, the Commission of Biological Standardization has not felt that complete separation into follicle-stimulating and luteinizing fractions was sufficiently assured to warrant establishing international standards for material from this source. None of the active substances of the anterior lobe has been prepared to similar degrees of purity.

A large number of preparations of the anterior lobe are on the market, but none of them has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association because of the lack of suitable evidence that such preparations are of value in therapy. The

119. Fellows Nutting, M.D.: The Antigonadrotropic Hormones in Normal Human Blood Serum, Endocrinology **26**:369-376 (March) 1940.

120. Rutherford, R. B., and Griffith, J. Q., Jr.: Pitressin-Inhibiting Substance in Serum of a Patient with Transient Diabetes Insipidus, J. Clin. Endocrinol. **1**:916-917 (Nov.) 1941.

commercially available preparations are relatively crude in comparison with those developed experimentally. They usually contain significant amounts of several other factors besides the one for which they are intended to be used. Inert proteins usually are present also. Furthermore, it has been shown that the active substances of many of these preparations deteriorate on standing in solution. D'Amour,[121] with his co-workers, has demonstrated that preparations of the anterior lobe purchased in drug stores have little demonstrable activity.

Extracts of the posterior lobe of the pituitary gland containing the oxytocic and the pressor factor are well known to clinicians. Their uses have been outlined. A number of preparations containing both factors, as well as preparations containing each factor, have been accepted by the Council on Pharmacy and Chemistry.[122] Their source is the pituitary glands of slaughtered animals, and they are assayed in terms of U. S. P. units. These are standardized to an international pituitary powder.

102 Second Avenue Southwest.

121. D'Amour, F. E.: The Potency of Certain Commercial Hormone Preparations: Second Study, Endocrinology **26**:88-92 (Jan.) 1940.

122. Freed, S. C.: Present Studies of Commercial Endocrine Preparations, J. A. M. A. **117**:1175-1182 (Oct. 4) 1941.

Book Reviews

Ambassadors in White. By Charles Morrow Wilson. Price, $3.50. Pp. 372, with illustrations. New York: Henry Holt & Co. Inc. 1942.

The subtitle of this most interesting book is "The Story of American Tropical Medicine," belying somewhat the more catchy phrase "Ambassadors in White." The subtitle, in truth, tells the story more properly than does the main title. The ambassadors in white are Finlay of Cuba, Reed of Virginia, Gorgas of Alabama, Deeks of Canada and Noguchi of Japan, together with the people with whom they were connected and with whom they worked. About half of the book is devoted to short biographic sketches of these five men, the ambassadors in their tropical garb. The rest of the book has to do with life, sickness and disease in the tropics and in Central America. The book is prefaced by a historical review, in which, incidentally, the author brings out many interesting facts. Probably few physicians realize that the first hospital in the Western Hemisphere was opened eleven years after Columbus' epochal voyage. Hospitals were established in Puerto Rico, Cuba, Panama, Mexico, Chile, Colombia, Ecuador and Venezuela prior to the beginning of the seventeenth century, and twenty-seven years before John Harvard was born the University of Mexico, Mexico City, had a chair of medicine. In 1538 the University of Santo Tomás, on the island of Santo Domingo, had started to teach medicine. A medical school was established in Lima, Peru, in 1621, antedating by many years the inauguration of formal medical teaching in the United States.

The biographies of the five heroes of the book are interesting and instructive. To most medical readers Gorgas is well known, as are his accomplishments and his life; the same may be said of Walter Reed and Noguchi, but Carlos Finlay, who for years prior to Reed's investigations advanced the theory of transmission of yellow fever by a vector, Aedes aegypti, is known only in a general way, while Deeks, of the United Fruit Company, is also known by name and reputation, but few persons know of his real accomplishments and his deeds. It is interesting to read about these two men who stand out as pillars in the story of medicine in the tropics. Deeks is responsible for the inauguration of sanitation and the fighting of disease on the United Fruit Company plantations. His accomplishments are altogether remarkable. To the United Fruit Company and to the Standard Oil Company Wilson pays tribute. These two great international business organizations in the tropics were motivated by an altruistic-economic desire to keep their employees well; they do and have done so. On the other hand, innumerable United States corporations in the past have gotten what they could get out of the Central American countries but have done nothing to advance the health of the natives and apparently have left behind them only ill feeling.

In the tropics of the Middle American countries the health conditions are distressing and deplorable, despite the fact that these countries per unit of population spend much more for public health than does the United States. The microscopic animal and vegetable life of the tropics grows freely and unrestrainedly, and as the vegetation is lush and rich, just so are the disease-carrying fungi and animal parasites unrestrained in their growth in an environment which gives them everything they need in the way of moisture, temperature and food. Then there are few physicians in these countries, and most of them have congregated in the larger cities, so the rural population does not have medical services except to a limited extent. The picture that Wilson paints is depressing, but education and enlightenment of the poor people are doing, and will do, much to combat the disease scourges which cause tropical inhabitants to die in early life or to become chronic invalids.

It might be said that the book is attractively written, reads easily and gives many data which are at the present time not only well worth while but of great

value to members of the medical profession and more particularly to the physicians who may have to serve in the armed forces of the United States in these tropical countries.

Advances in Internal Medicine. Edited by J. Murray Steele,. Vol. 1. Price, $4.50. Pp. XI + 292, with 16 illustrations. New York: Interscience Publishers, Inc., 1942.

Recently a tabulation was made of the age distribution of physicians in the United States. Nearly half of them, it appears, are less than 45 years old. Thus, if a mathematical formula can be applied to the writing of medical books, half of them should be compiled for the benefit of the younger men and insofar as possible by them.

Usually this is not the case. The modern multiauthored textbooks tend to be written by older men in what Sir Andrew Clark termed the cakes-and-ale stage of their careers. Perhaps this lends experience and dignity to the printed result, but at the same time the stimulating flavor of youth is lacking.

The first volume of "Advances in Internal Medicine" is particularly noteworthy because of its ten contributors the most venerable is 45 years old and several are still on the right side of 35. The purpose of the series is to supply from time to time an informal summary of progress in those fields of internal medicine in which progress has recently occurred. The topics in volume 1 are well chosen to carry forward this idea. They include the use of the Miller-Abbott tube, of insulin and protamine insulin and of sulfonamide compounds in the treatment of infection; to be up to date and sailing with the prevailing medical wind, the volume includes discussions of current ideas on hypertension, riboflavin deficiency and nephrosis.

The result is a satisfactory book, readable, authoritative and, above all, youthfully vigorous. If the editor continues to collect for the ensuing volumes of the series an equally alert and capable group of young writers, his venture will be successful. Physicians in practice will like it. But more particularly the eighty-odd thousand medical students and young practitioners for whom the series is really designed will feel that they are being spoken to by their favorite and most stimulating instructors in just the manner they most enjoy.

The Electrocardiogram and the X-Ray Configuration of the Heart. By Arthur A. Master, M.D.; Cardiologist to the Mount Sinai Hospital; Assistant Professor of Clinical Medicine, Columbia University. Second edition, enlarged and revised. Price, $7.50. Pp. 404, with 163 illustrations. Philadelphia: Lea & Febiger, 1942.

The same painstaking effort that went into the first edition of this book may be found in the revised and enlarged second edition. New material has been added. New sections deal with visualization of the chambers of the heart, disease of the tricuspid valve, myxedema and the "giant left auricle." The book covers rather thoroughly the effect of various types of cardiovascular disease and disorders on the cardiac silhouette. Each type of disease or disorder is illustrated by a roentgenogram of the heart. Beside each roentgenogram is placed an electrocardiogram. Each electrocardiogram is interpreted in the light of knowledge gained by the roentgen study plus a clinical study of the patient. The photographs and illustrations, which make up virtually the entire book, are excellent.

The main criticism of the book centers around the author's overenthusiastic interpretation of the electrocardiograms. The reader is left with the impression that in a given case one might learn the whole story by a careful study of the tracing alone. Numerous instances of this broad interpretation occur throughout the book. For example, the electrocardiograms in figures 49 *A* and 82 *A* are similar, indeed. Yet one is shown as the curve characteristic of rheumatic heart disease with mitral stenosis and insufficiency, while the other represents the curve characteristic of exophthalmic goiter.

With the exception of the excess of enthusiasm in the interpretation of tracings, the book is excellent.

Treatment in General Practice. By Harry Beckman, M.D., Professor of Pharmacology, Marquette University School of Medicine. Fourth edition, thoroughly revised. Price, $10, cloth. Pp. 1,015. Philadelphia: W. B. Saunders Company, 1942.

The fourth edition of this book contains much new material—so much, indeed, that it cannot be entirely listed by the reviewer. It should be enough to say that the work has been brought thoroughly up-to-date. When one finds mention of sulfanilylguanidine and sulfacetamide, one realizes the newness.

The book is divided into twenty-four general sections in which the treatment of various diseases is discussed. The author comments on the great wealth of contributions to the therapy of disease that have appeared in recent years, and he speaks of the difficulty in selecting the worth while material, but he has done an excellent job. He has shown his ability to retain the oldest forms of treatment when they are adequate, as well as to evaluate properly the advantages (and disadvantages) of the sulfonamide compounds most recently introduced as therapeutic agents.

His good common sense and forthright criticism of unsound procedure are noticeable throughout the book. It must be difficult to inject a sense of humor into a solemn medical treatise, but the author has done so, and successfully, too.

The book is well written and is easy and pleasant to read. Altogether, the author has done remarkably well in putting a great deal of sound and worth while information into a relatively small space.

Central Autonomic Regulations in Health and Disease. By Heymen R. Miller, M.D., with an introduction by John F. Fulton, M.D. Price, $5.50. Pp. 440. Greene & Stratton, Inc., New York, 1942.

This is a work for which many clinicians have been waiting. The author, well qualified for the task, presents the principal evidence bearing on the relation of hypertension, disturbances of metabolism and other diseases to disturbances, especially central disorders, of the autonomic nervous system. All fields of medicine, as the author writes, especially those of internal medicine and neurology, impinge on a common territory here—a common ground of central autonomic regulations.

After a brief introduction, which relates to the general physiology of the autonomic nervous system, the author considers in turn the part played by this system in maintaining the homeostasis of body temperature, metabolism, circulation, respiration and other phases of human physiology and disease. The response of the autonomic nervous system to pharmacodynamic substances receives attention in later chapters, and discussion of anatomic aspects at the end provides a satisfactory and interesting means for summarizing the material as a whole.

Complete documentation, as well as impartial consideration of opposing interpretations, adds greatly to the value of this work. The book can be highly recommended.

The Surgery of Pancreatic Tumors. By Alexander Brunschwig. Pp. 397, 123 illustrations and 1 color plate. St. Louis: C. V. Mosby Company, 1942.

Written with the view of dealing with relatively few facts in a newly developed field," and thus serving "to stimulate further work in this field," this monograph represents the author's attempt to record the cumulative "experiences in the surgery of all types of pancreatic tumors." The book is divided into twenty-seven chapters, the first few of which are devoted to the historical development of the subject; the embryologic, anatomic and physiologic aspects of the pancreas; experimental studies; diagnostic procedures, and preoperative and postoperative care. Four chapters are concerned with benign and with malignant pancreatic cysts and four chapters with benign and with malignant tumors of the ampulla of Vater. The remaining chapters deal with solid tumors of the pancreas, especially the malignant forms. An extensive bibliography arranged alphabetically

is placed at the end of the book. The illustrations, consisting of photographs and line drawings, are profuse, well selected and instructitve. In this monograph, which is undoubtedly the most comprehensive consideration of the subject to date, the author fulfills his purpose thoroughly and successfully.

Die Thrombocyten des menschlichen Blutes und ihre Beziehung zum Gerinnungs- und Thrombosevorgang. By A. Fonio and J. Schwendener. Pp. 130, with 112 illustrations. Berne: Hans Huber, 1942.

Professor Fonio, whose studies on blood platelets have been continuously appearing since 1911, has, with an associate, summarized in a small concise monograph his recent efforts to visualize the process of coagulation with an ultramicroscope under dark field illumination. There are truly remarkable photographs of the resting and the irritated thrombocyte, of the growth of pseudopodia, of the agglutination of platelets followed by the liberation of vesicles containing thrombokinase and, finally, of the precipitation of needles of fibrin as the end point of thrombosis. This work is all the more remarkable as it provides a morphologic basis for physicochemical phenomena. It proves that purely morphologic investigations, undertaken with improved technics, still play an important part in the furthering of knowledge. The senior author, who is professor of surgery at the University of Bern, does not draw any practical conclusions from his studies; he seemingly wished to emphasize the central role of the blood platelet in the process of thrombosis.

Love Against Hate. By Karl Menninger, M.D. Price, $3.50. Pp. 311. New York: Harcourt, Brace & Company, 1942.

Dr. Menninger's thesis, in brief, seems to be that the restrictions which have grown up under the customs and manners of "civilization" serve early to inculcate hate as a dominant trait of human character. The infant forced to nurse at regular hours and annoyed by attempts to train the excretory habits soon comes to hate his mother. Ingrained hates also develop in women, frustrated in all sorts of ways. The devotee of chess is really a father hater; he is pursuing a dominating male character, the king. This universal hate, if the reviewer understands the author correctly, has much to do with the disabilities of modern life, including the promotion of war. Love, fostered by work and by play, is set forth as an antidote. The reviewer does not follow Dr. Menninger in all the ramifications of his thesis, but he agrees that material and mechanical advances have not solved the problem either of human happiness or of behavior. Idealism, the mystical appreciation of intangible values, seems to be necessary, as is clearly realized by all great prophets, to preserve man from being evolution's failure.

News and Comment

Hermann M. Biggs Memorial Lecture.—Lieut. Col. Paul F. Russell will deliver the Hermann M. Biggs Memorial Lecture on Thursday, April 1, 1943 at 8:30 p. m. in Hosack Hall, New York. The title of the lecture will be "Malaria and Its Influence on World Health." The lecture is to be given under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine and will be open to the public.